A Dissertation on

PREVALENCE OF DYSLIPIDEMIA AMONG HIV INFECTED PATIENTS USING FIRST LINE HAART IN COIMBATORE MEDICAL COLLEGE HOSPITAL

Dissertation Submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

With partial fulfillment of the regulations
for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE,
COIMBATORE
APRIL 2015

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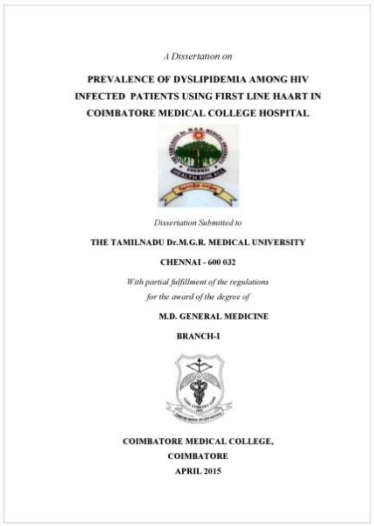

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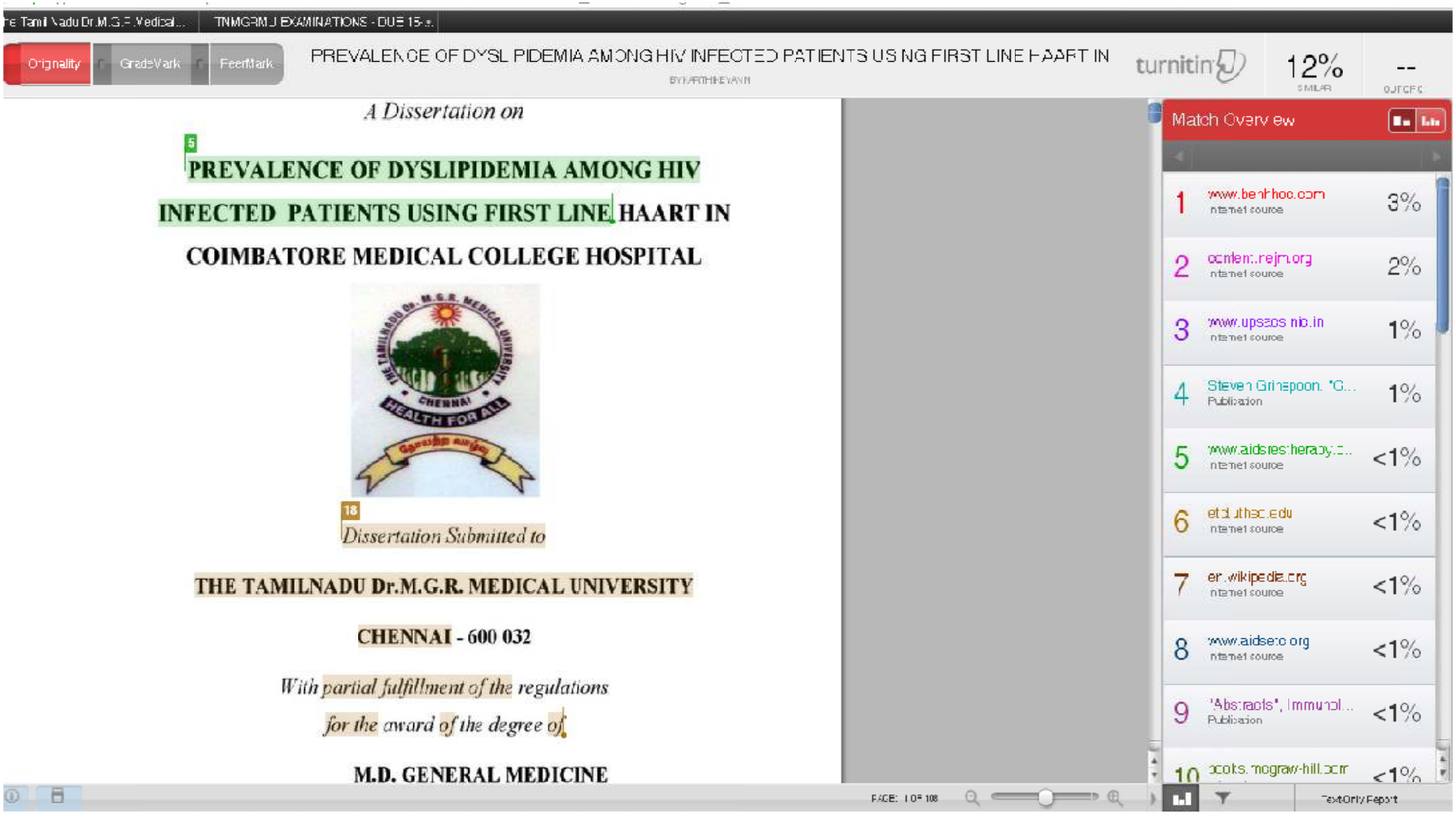
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DECLARATION

I solemnly declare that the dissertation titled **" PREVALENCE OF DYSLIPIDEMIA AMONG HIV INFECTED PATIENTS USING FIRST LINE HAART IN COIMBATORE MEDICAL COLLEGE HOSPITAL"** was done by me from AUGUST 2013 TO JULY 2014 under the guidance and supervision of Professor **Dr. M.RAVEENDRAN. M.D.** This dissertation is submitted to **The TamilnaduDr.M.G.R.Medical University** towards the partial fulfilment of the requirement for the award of MD Degree in General Medicine(Branch I).

Place: Coimbatore **DR. KARTHIKEYAN.N.**

Date :

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LIST OF ABBREVIATIONS USED

1. HIV	–	Human immunodeficiency virus
2. AIDS	–	Acquired immuno deficiency syndrome
3. HAART	–	Highly active antiretroviral therapy
4. ART	–	Antiretroviral therapy
5. NRTI	–	Nucleoside reverse transcriptase inhibitor
6. NNRTI	–	Non Nucleoside reverse transcriptase inhibitor
7. PI	–	Protease inhibitor
8. PLHA	–	People living with HIV and AIDS
9. NACO	–	National AIDS Control Organisation
10. 3TC	–	Lamivudine
11. CAD	–	Coronary artery disease
12. TNF	–	Tumor necrosis factor
13. IFN	–	Interferon
14. PPAR	–	Peroxisome Proliferatory Receptor Gamma
15. STD	–	Sexually transmitted diseases
16. SREBPI	–	Sterol Regulatory Enhancer – Binding Protein
17. CRF	–	Circulatory Recombinant forms
18. HLA	–	Human leucocyte antigen
19. GALT	–	Gut associated Lymphoid tissue
20. ELISA	–	Enzyme Linked Immunosorbent Assay

21. GLA – Generalised Lymphadenopathy

22. CDC – Centre For Disease Control

23. LDL – Low density Lipoprotein

24. HDL – High density Lipoprotein

25. TC – Total Cholesterol

26. TGL - Triglycerides

27.CMCH - Coimbatore Medical College Hospital

28.CBE - Coimbatore

CONTENTS

ABSTRACT

INTRODUCTION:

AIDS is a multifactorial disease caused by HIV virus, which suppresses the immune system leading to life threatening opportunistic infections and cancers. Without treatment the average survival time is around 9 – 11 yrs.The introduction of HAART therapy leads to decreased mortality and morbidity in developing countries.Eventhough the HAART therapy is beneficial in decreasing the morbidity , the complications of which is now emerging as a biggest problem in the present scenario.

METHODOLOGY :

Among the patients attending CMCH ART centre ,totally 100 patients with age between 18 – 60 yrs were included in the study.Among them one group on HAART with 50 patients and the rest 50 patients in non HAART group were equally divided.Among HAART group ,they were further subdivided based on regimens .All the 100 patients were followed up with lipid profile values at baseline,6 months and 12 months. These values were analyzed and compared by statistical methods .

RESULTS :

As observed by the study there occurred a significant lipid abnormalities in patients on HAART.There is a statistically significant increase in total cholesterol, triglycerides, LDL among the HAART patients at the end of one year. However there is statistically insignificant decrease in high density lipoproteins in HIV infected patients on HAART.Prevalence of dyslipidemia is more in efavirenz based regimen. From the results obtained in our study it is clear that the prevalence of dyslipidemia(elevated TC, TGL & LDL) was higher in patients on ART patients when compared to non ART patients (p value < 0.001). There was no difference in the prevalence of HDL.

In conclusion by monitoring the lipid parameters in HIV patients to be started on HAART, better to start with lipid friendly drugs if there is associated dyslipidemia, on the other hand the patients with dyslipidemia who was already on HAART can be switched over to lipid friendly regimens or we can add lipid lowering drugs . So by doing this we can prevent the cardio and cerebrovascular complications and thereby we can improve the quality of life in patients who are already immunocompromised.

KEY WORDS : HIV, AIDS, HAART, Non HAART , DYSLIPIDEMIA

INTRODUCTION

HIV is a lentivirus(a subgroup of retrovirus) that causes AIDS, a condition in humans which causes a progressive failure of the immune system that leads to life threatening oppurtunistic infections and cancers.Without treatment the average survival time after infection with HIV is estimated to be 9 – 11 yrs.

The immune cells infected by HIV are Helper- T cells, macrophages, dendritic cells. HIV infection causes low levels of CD4+T cells by many mechanisms that includes apoptosis of uninfected bystandercells, direct killing of infected cells, killing of infected CD4 cells by CD8 cytotoxic T cells. HIV-I has high virulence and high infectivity where as HIV-II has low virulence and low infectivity

The introduction of HAART had led to a dramatic reduction in AIDS related morbidity and mortality in both developed and developing countries. HIV replication plays an important role in its course of disease. Suppression of replication is very important to prevent HIV associated morbidity and mortality.

Strict adherent to ART therapy will cause adequate suppression. Since the Introduction of HAART patient started to have a improved quality of life but however comorbid problems have been emerged. Dyslipideamia, insulin resistence & Diabetes are some of the metabolic complications of long term use of HAART.

AIMS AND OBJECTIVES

Aim of the study

To analyze the lipid abnormalities in adult HIV patients on HAART therapy

Objectives

1) To determine the prevalence of dyslipidemia in HIV patients on HAART therapy
2) To compare the lipid profiles of HIV patients on HAART therapy and those who are not started on HAART therpy.

REVIEW OF LITERATURE

HISTORY OF HIV

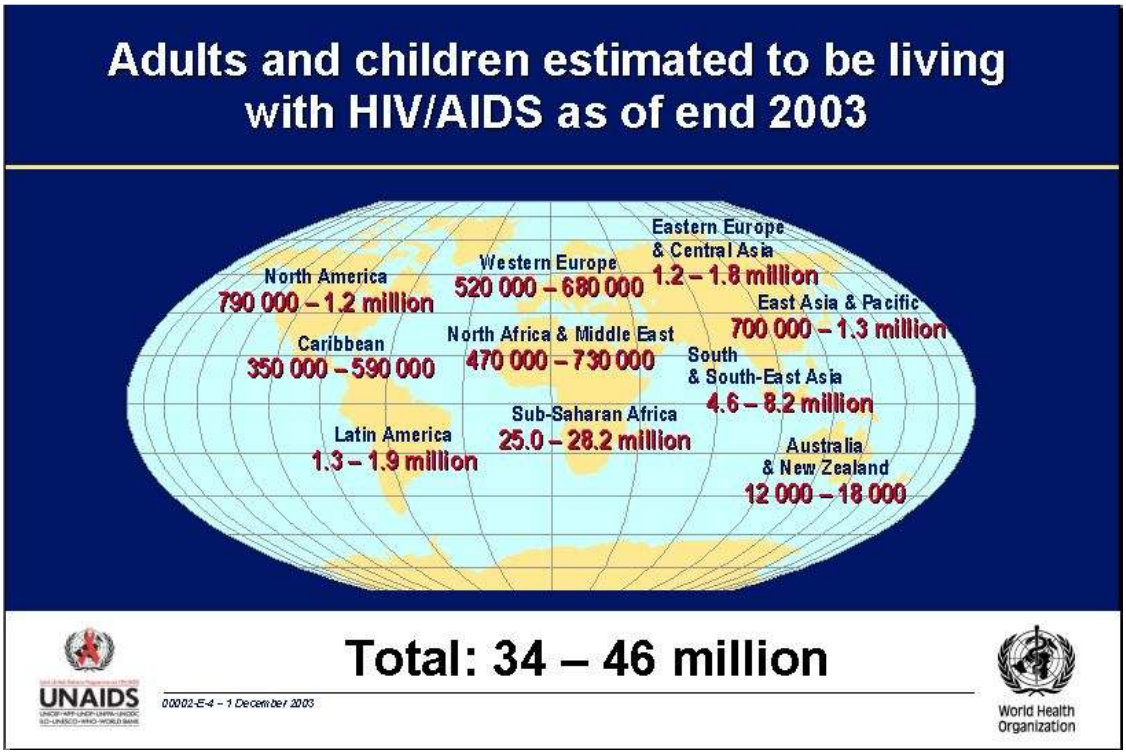
In 1970s a syndrome called fading kitten syndrome caused by feline leukemia virus characterized by immunodeficiency was identified.

In 1981 the virus Human T cell leukemia virus was discovered and found to cause T cell leukemia in human beings. Also in 1981 pnenmocystis carinii pneumonia was reported in homosexual men. In 1982 the hemophiliacs has contracted this disease. In may 20th 1983 a retro virus was isolated from AIDS patient with GLA by Luc montagnier and he named it as lymphadeopathy associated virus. Another RETRO virus was isolated from AIDS patient similar to HTLV and they called it as HTLV – III in may 4th 1984 by Robert C Gallo and his colleagues.

In 1984 the industrialised countries screening for HIV in blood donors. The working definition for AIDS was given by centre for disease control in 1986.

Also in this same year the International committee for taxonomy of viruses -7 has renamed HTLV- III / LAV as Human Immuno deficiency virus

EPIDEMIOLOGY



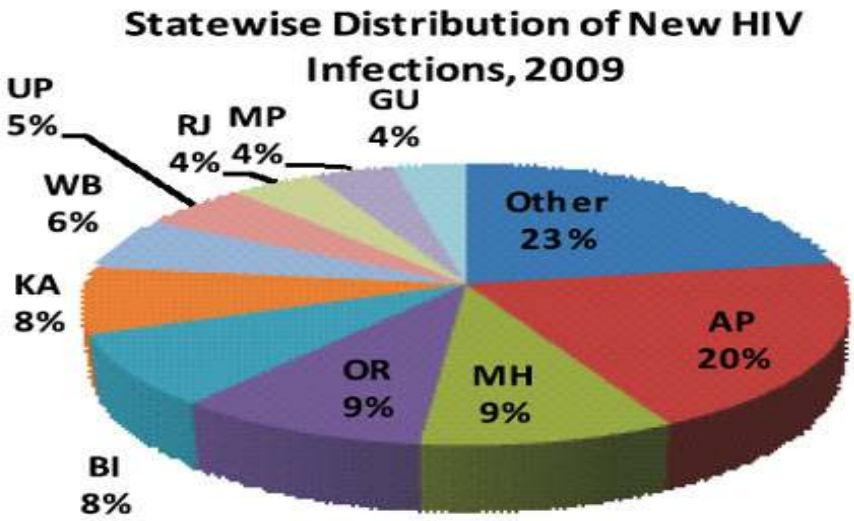
HIV infection is global pandemic. According to UNAIDS there will be 33.3million Individuals were living with HIV infection at the end of 2009. About more than 95% of the people living with HIV/AIDS resides in low and middle income countries, of that 50% will be female and 2.5million are children less than 15 years. In 2009 the global AIDS deaths was totaled around 1.8million that includes 2,60,000 children less than 15years. HIV epidemics has occurred in waves in different regions of the world. More than 2/3rd of all peoples with HIV infections live in

sub Saharan Africa that has only 10-11% of the worlds population, within that the southern Africa is worst affected. Heterosexual exposure is the most common mode of transmission there.

In east, south and south east Asia are mostly affected. Among the Asian countries, Thailand has an adult seroprevalance rate of >1%. In Bangladesh and Pakistan the prevalence has increased very much

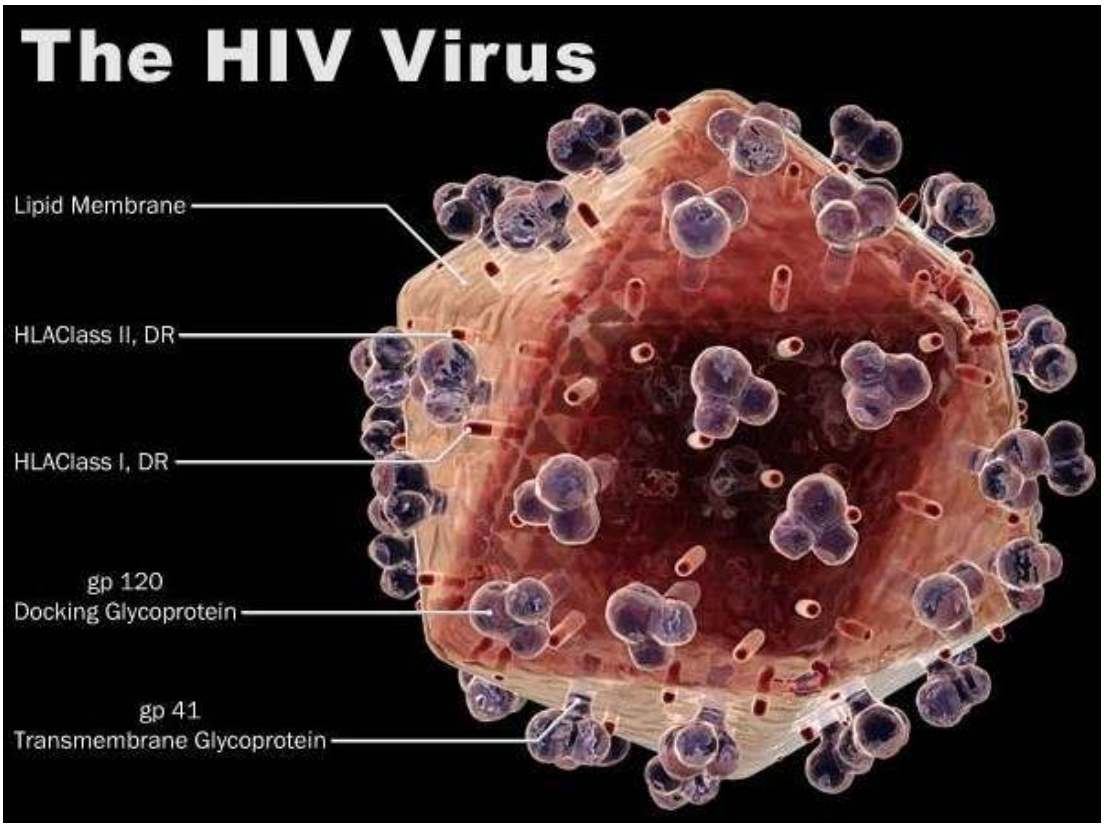
In united states as of jan 2010, the total cases estimated was 1,108,611. Around 1.1 million individuals were living with HIV infection of which 21% are unaware of the infection. Around 48% were men who have sex with men. An estimated 56,000 individuals are newly infected each year.

In India the first case of AIDS was reported in the year 1986. 2.4million Peoples are living with this condition. About 1,70,000 AIDS related deaths happened. New HIV infections has declined by more than 50% over the past decade from 2.7 lakh in 2000 to 1.2lakh in 2009. Adult HIV prevalence in India is 0.27% as of 2011. Over all India's HIV epidemics slowing down with 57% decline in new infections between 2000-2011 and a 29% decline in AIDS related deaths between 2007-2011.



MORPHOLOGY

HIV as mentioned previously is a RETRO virus belonging to subfamily of LENTI virus. HIV virion is an icosahedral structure that contains numerous external spikes which are formed by 2 major enveloped proteins namely gp120 and gp41.

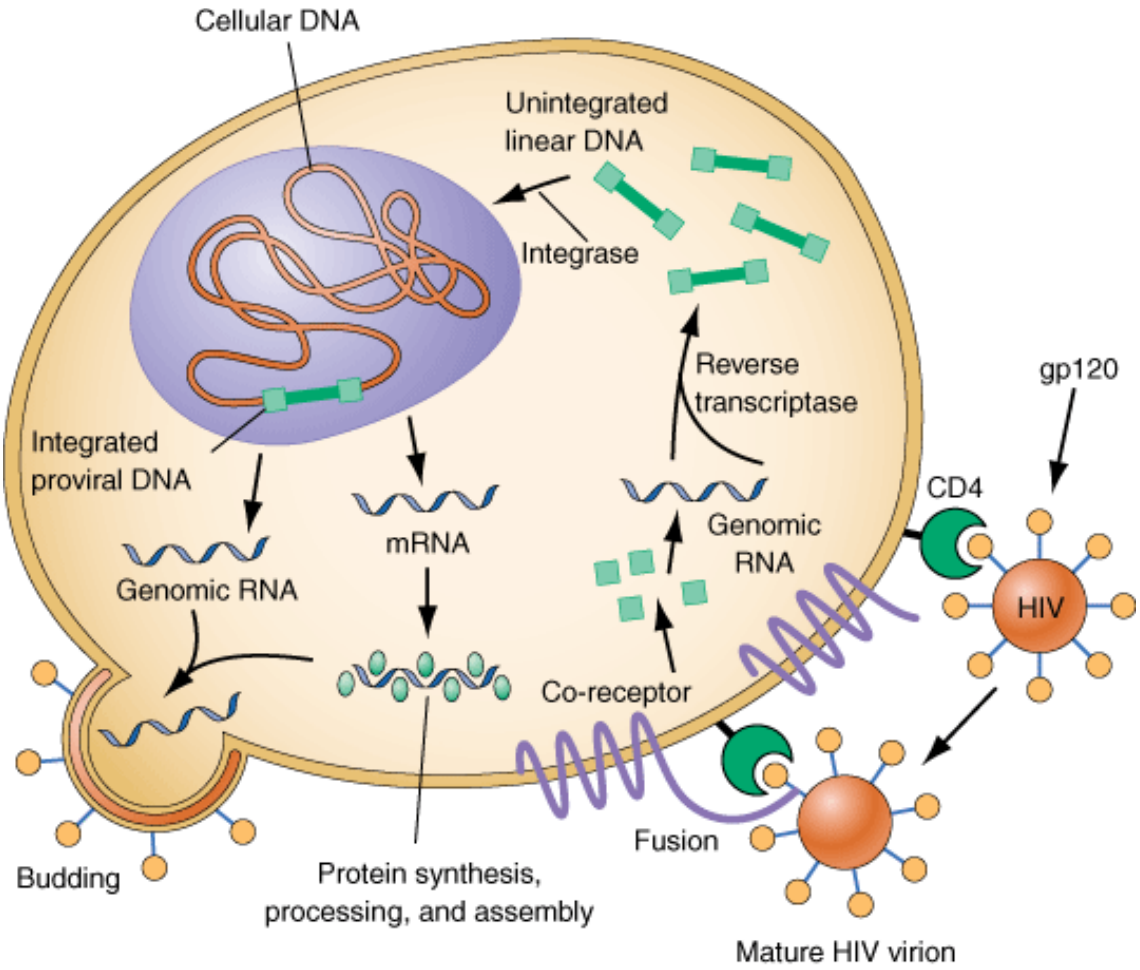


REPLICATION OF HIV

HIV is a RNA virus. Replication cycle of HIV starts with the binding of Gp120 protein to its receptor on the host cell surface that is the CD4 helper cells. As soon as the gp120 binds to CD4 there will be a change which facilitates binding to one of its co-receptors namely CCR5 and CXCR4. Dendritic cells also will facilitate the binding of the virus to the CD4 cells.

After the binding of gp120 with CD4 cells there will be a fusion with the host cell membrane through gp41 followed by coiling that brings virion and target cell together. Following fusion the complex composing viral RNA and enzymes surrounded by a capsid protein is released into the cytoplasm of the target cell. During the traversion of the preintegeration complex to the nucleus from the cytoplasm the viral reverse transcriptase enzyme catalyses the reverse transcription of RNA to DNA and the protein coat release the double stranded proviral HIVDNA. The viral DNA access the nucleus pore and is exported from cytoplasm to the nucleus. In the nucleus it is integrated into host cell chromosomes by the enzyme integrase. The replication and pathogenesis of HIV disease is mainly mediated by cellular activation. Unless this cellular activation takes place there won't be efficient integration of viral DNA to the host cell. This cellular activation is also mainly responsible

for transcription of proviral DNA into genomic RNA or mRNA. After transcription there will be translation of HIV mRNA into proteins which undergoes various modifications, then the proteins, enzymes, genomic RNA forms the viral particle. Finally the cleavage of gag pol precursor that yields a mature virion is catalysed by virally encoded protease.



HIV GENOME:

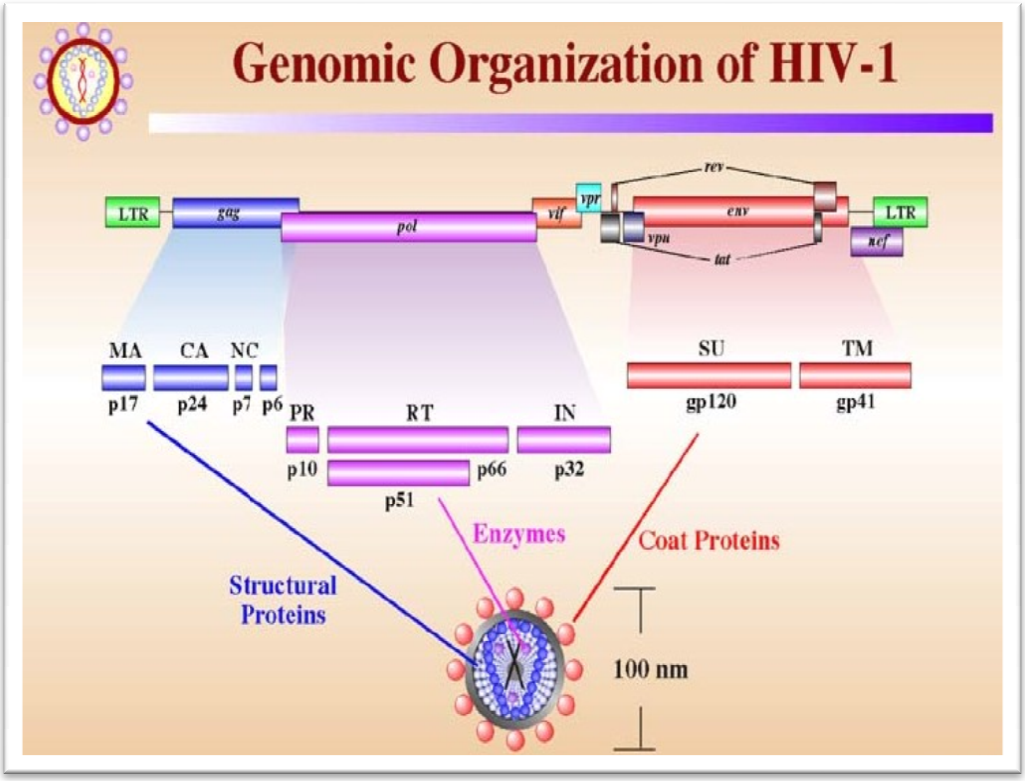
HIV - I contains gene that encodes protein

Gag - core

Pol - protease processing of viral protein reverse transcription and integration

Env - envelope glycoprotein

Also contains 6 other genes (tat, rev, nef, vif, vpr, vpu) which plays an important role in pathogenesis of HIV disease.



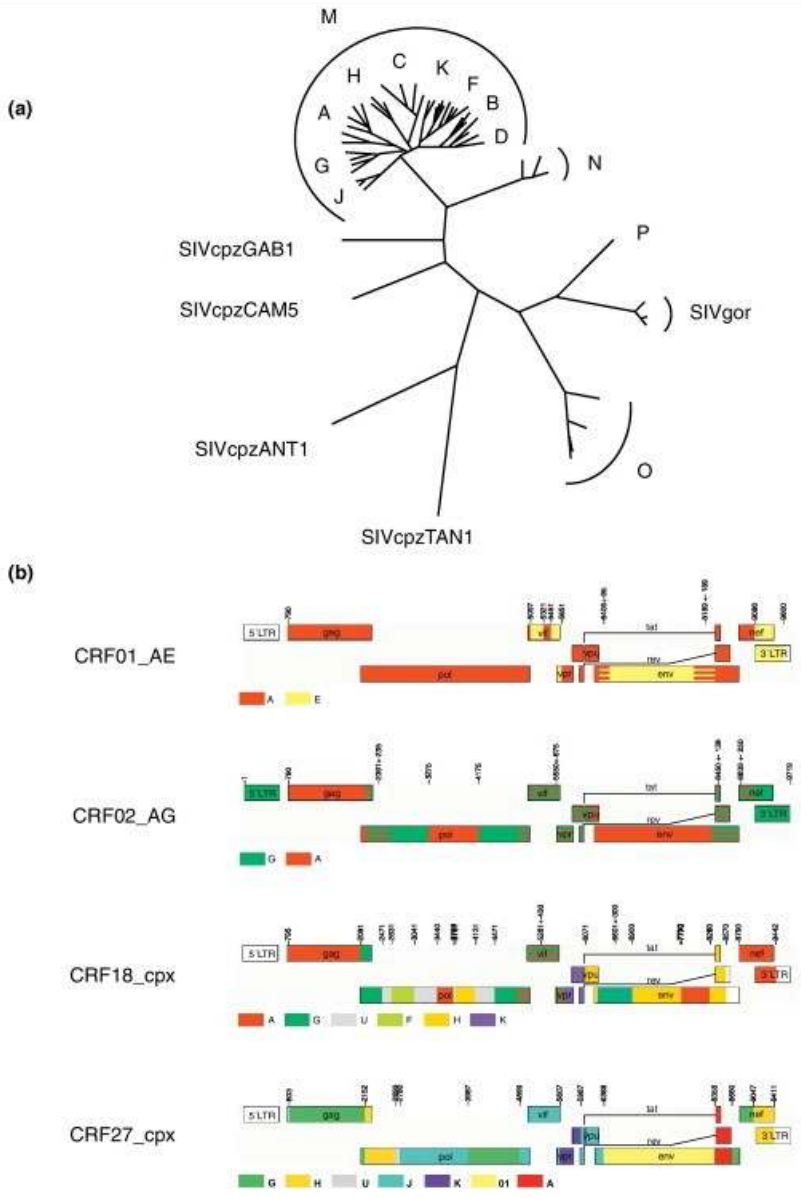
The main gene differentiation between HIV-I & II is that HIV-II has no vpu and HIV-I has no vpx.

MOLECULAR HETEROGENECITY OF HIV:

There are variable degree of differentiation ranging from 2% to 50% in coding sequences of viral envelope protein. HIV virus can evolve by several means that includes basal substitution, insertion, deletion, recombination and gain and loss of glycosylation sites. The balance

between immune pressure and functional constrains on proteins influences the regional level of variation within proteins. There are four groups of HIV-I , group-M the most common and the group-O relatively rare followed by group-N and group - P. on comparison with other LENTI viruses HIV-I is very closely related to viruses isolated from chimpanzees and gorillas. The M group comprises of 9 subtypes as well as circulating recombinanat forms. These CRFs are formed by two subtypes that infect the same individuals which then recombine that creates a virus with a selective advantage.

About 7 strains of HIV has a global prevalence of >2.5% which accounts for majority of infections. Subtype C virus are the most common form worldwide that accounts for 50% prevalence of infections. In Asia HIV-I isolates of CRF01_AE lineage and subtypes C and B predominates. The most common infection in south and south east Asia is by CRF01_AE, but subtype C is common in India. Various faces of HIV that includes multiple subtypes, CRFs, continuous viral evolution has implications for different rates of disease progression, response to therapy and drug resistance



RISK GROUPS AND MODE OF TRANSMISSION

HIGH RISK GROUPS:

Female sex worker

Men who have sex with men

Transgender

Intravenous drug abusers

BRIDGE POPULATIONS:

Truckers

Migrant populations

MODE OF TRANSMISSION:

Heterosexuals – 88.2%

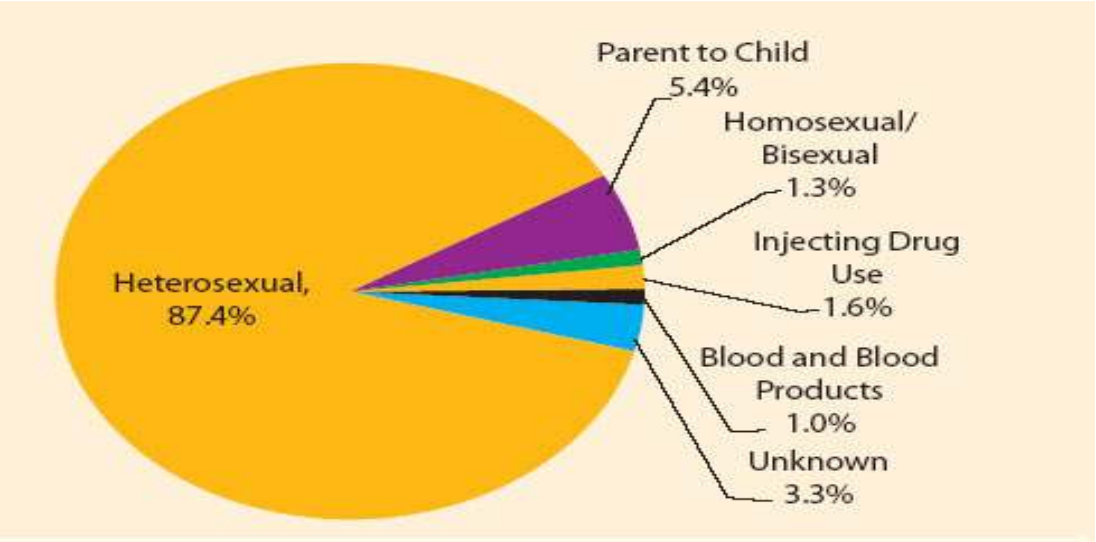
Parent to child – 5%

Homosexuals – 1.5%

Intravenous drug abusers – 1.7%

Blood and blood products – 1%

Not specified – 2.7%



PATHOPHYSIOLOGY AND PATHOGENESIS:

The hallmark of HIV disease is a profound immunodeficiency that results from a quantitative and qualitative deficiency of the T lymphocytes called as helper T cells that is CD4 cells. There are two co-

receptors that HIV uses for its binding, fusion and entry. They are known as CCR5 and CXCR4.

The various mechanisms that involved in cellular deletion and immune dysfunction are direct infection, destruction of the cells by HIV, immune clearance of infected cells, aberrant cellular activation and activation induced cell death. Both viral and immunogenic events which occurs during the full course of the disease are complex. The pathophysiologic events of HIV disease are multifactorial and they are different at different stages of the disease.

EVENTS IN HIV INFECTION

The disease is primarily transmitted through sexual contact and so the main site of portal of entry for HIV virus is through mucosal surfaces. This includes oropharynx, rectum, genital mucosa. These are the areas that are rich in langerhans and dendritic cells which traps the antigens and viral particles. The antigens are trapped by the dendritic cells through DC-SIGN receptors which is involved in transportation of virus to the draining lymphoid tissues, within few hours after exposure to the virus there will be quick multiplication of virus which may be detected in the draining lymph nodes. The minimum time period required for infection is two hours contact period between simian

immunodeficiency virus and vaginal mucosa. After within few days the virus can be detected in nearby lymphocytes,monocytes and then in the regional lymphoid tissue. Followed that the primary viremia leads to full dissemination of virus throughout the body.

ESTABLISHMENT OF CHRONIC AND PERSISTENT INFECTION:

PERSISTENT VIRAL REPLICATION:

Eventhough the humoral and cellular immune responses are activated following primary infection the virus escapes immune mediated clearance and is never completely eliminated from the body. Within a median of ten years a chronic infection sets in which is a hallmark of HIV disease,followed which patient becomes ill. Throughout his chronic infection the viral replication takes place continuously which can be detected by highly sensitive assays in the circulation and the lymphoid tissues. Chronicity seen in HIV infection are also seen in HCV and HBV infection,but the immune system is not the target for these viruses.

EVASION OF IMMUNE SYSTEM CONTROL:

This virus evades from the immune system by various mechanisms. The main one is by establishment of continuous viral replication with generation of viral diversity via mutation and

recombination. The clones of CD8 cytotoxic T cells that are produced and expanded during primary HIV infection are deleted or made dysfunctional due to the persistent viral replication. Another mechanisms by which the virus escapes from immune system is by down regulation of HLA class I molecules on the surface of HIV infected cells by nef protein of HIV which results in the lack of recognition. The three mechanisms by which HIV evades from neutalising responses are hypervariability in the primary sequence, extensive glycosylation and masking of neutralising epitopes. Another important mechanism of evasion is sequestration of infected cells in immunologically privileged sites such as central nervous system. Since HIV primarily infects CD4 cells and so this loss of those cells have profound negative consequences for the immunologic control. This evasion of HIV from the immune response allow the formation of a pool of latently infected cells which cannot be eliminated by virus specific cytotoxic cells, so HIV succeeds in putting a strong basement creating a state of chronic infection

RESERVOIRS OF HIV INFECTED CELLS:

In all HIV infected indivuals there will be pool of latently infected resting CD4 cells which serves as atleast one component of persistent reservoir of virus. There are two latencies that are pre and post integration latencies. Eventhough the plasma viremia is suppressed to

less than 50 copies of HIV RNA/ ml by potent combination of ARTs, this pool of latently infected cells persists and produce replication competent virus. The main reservoir for HIV infected cells includes lymphoid tissue, the peripheral blood and CNS. The major drawbacks for the eradication of virus is mainly by these persistent reservoir of infected cells at various latent stages.

LYMPHOID ORGANS AND HIV PATHOGENESIS:

The main site for multiplication, establishment and progression of HIV infection are the lymphoid tissues. Eventhough the plasma viremia is accounted for the level of disease activity, the viral replication mainly occurs in lymphoid tissues. The cellular response and immune activation are mainly reflected by lymphadenopathy. Our recent studies have focused on GALT that is Gut Associated Lymphoid Tissue, where the earliest viral replication occurs. Normally in the early stages of HIV , the germinal centre is generally preserved. The follicular dendritic cells traps the antigens and present it to the B cells which is the normal physiologic function. In case of HIV the trapped virions causes secretion of proinflammatory cytokines such as IL1 beta, TNF alpha, IL6 which will upregulate the viral replication. CD4 helper cells which goes into germinal centres are susceptible to infection by these trapped virions. So in HIV infection the normal physiologic function of immune system is

affected. As the disease progress the germinal centre which was preserved early will undergo disruption and swelling, finally to cell death. In the advanced stage of disease there is complete disruption and resolution of FDC finally goes into stage of burn out. This destruction of lymphoid tissue effects both to inability to control replication and inability to make immune response.

ROLE OF CYTOKINES IN HIV PATHOGENESIS

Cytokines which are the components of immune system play an important role in regulation of HIV expression. The cytokine involved in the induction and enhancement of HIV expression are IL1, IL2, IL3, IL6, IL18, IL12, TNFalpha, TNFbeta, GM-CSF. In these IL18 play an important role in development of HIV associated lipodystrophy syndrome. TNFalpha, IL1beta and IL6 are the potent inducers of HIV expression. IFNalpha, IFNbeta, IL32 suppress the HIV replication. While TGFbeta, IL4, IL10, IFNgamma will induce or suppress HIV expression depending on the system involved. The elevation of TNFalpha and IL6 are demonstrated in plasma and CSF while TNFalpha, IL1beta, IFNgamma,IL6 are demonstrated in the lymph node. HIV replication is controlled by endogenous cytokines which acts synergistically in an autocrine and paracrine manner. Finally the secretion of some

proinflammatory cytokines is a result of aberrant immune activation seen associated with HIV infection.

GENETIC FACTORS IN HIV PATHOGENESIS

Several genetic variations have been now identified in human beings that influence the risk of acquiring HIV, rate of disease, progression, virological control and immune response. There are polymorphisms identified in genes in the MHC locus, chemokines , cytokines and other host factors. Recently they have identified polymorphisms within the HLA-B and HLA-C which is associated approximately 15% variation in viral load during the asymptomatic period. In some individuals MHC Class I and class II will predispose them to an immunopathogenic response particularly in some tissues like CNS, Lungs or against some HIV infected cell types such as macrophages, dendritic cells, langerhan cells. There is increased risk of transmission of HIV infection among heterosexual Zambian couples who have an alleles sharing at HLA-B locus. Also founded HLA heterozygosity for class-I loci are associated with delayed onset AIDS in HIV, where as in HLA homozygosity it was a reverse. Another gene called transporter associated with antigen processing (TAP gene) play an important role in predicting the outcome of HIV infection. It is also noted that individuals with haplotype 8.1 also been correlated with rapid

decline in CD4 T cells. Recent studies shows the single nucleotide polymorphism (SNP) in the killer immunoglobulin like receptor (KIR) was found to be strongly associated with rapid progression to AIDS. The best example for a genetic factor which influences HIV infection and pathogenesis is related to the gene which codes for CCR5 the major HIV co-receptor. There are individuals who remains uninfected even though after repeated sexual exposure to HIV even though in high risk situation. These individuals were found to have high resistance with R5 strins of HIV-I but they were readily infected with X4 strains. On various analysis these individuals inherited a homozygous defect in the gene that encodes for CCR5. They have a homozygous defect for CCR5 32 allele. 20% of European individuals are heterozygous for CCR5 32 allele and has partial resistance or a delayed disease course. Cohort studies from western, central Africa and far east asia has absent CCR5 32 allele

IMMUNE RESPONSE TO HIV

Both humoral and cellular immune responses play an important role in HIV disease. These immune response are directed against variable antigenic determinants of HIV.

HUMORAL IMMUNE RESPONSE

Usually the antibodies to HIV will appear within 3-6 weeks Almost invariably within 12 weeks of primary infection. Usually the neutralizing

antibodies appear after the initial decrease in plasma viremia. The antibodies that are detected first are those against envelope gp41 followed by gag protein p24 and gag precursor p55, gp 120 and gp 41 are the only enveloped proteins that elicit neutralizing antibodies. The neutralizing antibodies appears in first 6 months, but viruses escapes these antibodies. There are 2 types of neutralizing antibodies one is type specific antibodies that appears early infection and they neutralize the viruses of a given strain. The other one is group specific neutralising antibodies that appears late in infection, which they neutralisie a wide variety of HIV. There are 2 types of group specific neutralising antibodies one directed towards the CD4 binding site of gp120 and those binding to proximal region of gp41. Antibodies directed against gp120 and gp41 also participate in antibody dependent cellular cytotoxicity mediated killing of HIV infected cells. There is a entity called bystander killing in which the anti gp130 antibodies kills uninfected CD4 T cells complement also play an important role in humoral immune response.

CELLULAR IMMUNE RESPONSE:

Cellular immunity is mediated by CD4 T cells and CD8 T cells. In this CD4 T cells plays an important role in immune response by helping HIV specific B cells and CD8 T cells and of directly killing HIV infected cells. CD8 T lymphocytes cause the lytic destruction of target cells.

There are 2 types of cytotoxic T lymphocytes the first type directly lyses the target cells without prior invitro stimulation, the other type reflects the precursor frequency of cytotoxic T lymphocytes. It is also found that there is direct relation between the levels of CD8 T cells capable of producing IFN-gamma to HIV antigen and RNA levels. Some of the forms of cell mediated immunity to HIV described are CD8 T cell mediated suppression of HIV replication, antibody dependant cellular cytotoxicity and NK cell activity.

FACTORS INFLUENCING HIV DISEASE PROGRESSION

HOST FACTORS

Old age peoples have a rapid progression of the disease, but it was an independent predictor in IV drug abusers. The gender do not have any major influence over the disease progression. Ethnicity also does'nt have any influence. It has been studied that 5% of HIV patients will be clinically stable for about 10 or more years after seroconversion and they are called as long term survivors or long term non progressors.

COFACTORS

HIV patients with CMV seropositivity were found to have 2-4 fold higher risk of disease progression. This states that CMV is a cofactor in HIV patients which leads to disease progression. There is no clear cut data that EBV , HHV6, hepatits B, acts as a cofactor.

DEFECTIVE CORECEPTORS

To infect a cell HIV needs CD4 receptor. Another receptor needed to bind and infect the cells are called chemokine receptor named CCR5. In many individuals this CCR5 carry a mutant gene delta32 deletion. If the persons are homozygous to delta32 then they found to have less risk for the infection with HIV.

SDF-1 GENE MUTATION

Stromal derived factor-1 is a cytokine which normally binds to CXCR4. Individuals having mutation of the gene that produces SDF-1 are more resistant to infection.

OTHER POTENTIAL COFACTORS

Association between smoking and CD4 lymphocyte loss or more rapid disease progression were founded in some studies. In developing countries it was studied that malnutrition may accelerate the HIV disease progression.

MARKERS FOR HIV DISEASE PROGRESSION

Certain measurable traits helps in disease staging and predicting susceptibility to opportunistic infections.

BETA2 MICROGLOBULIN

It is a non specific marker of immune activation. High titre levels are seen in association with disease progression. Also higher levels are found in various viral infection and in patients with lymphoma.

NEOPTERIN

Derived from macrophages and B lymphocytes. It is estimated using liquid chromatography and radio immunoassay. It also predicts the disease progression. Other conditions having elevated neopterin levels are collagen vascular disorders, malignancies and some infection.

s IL- 2R

High levels of s IL -2R found in patients with AIDS and it correlate negatively with CD4 cell counts.

SOLUBLE CD8

It is an early marker of HIV infection and levels correlate with number of CD8 lymphocytes.

ANTI p 24 ANTIBODY

Poor prognosis is seen in patients with declined anti p24 antibody.

ANTI gp 120 ANTIBODY

Absence of the antibody is related to disease progression.

p24 ANTIGEN

It is transiently seen in acute stages of HIV infection and in latent stages of HIV disease. A low CD4 count with p24 antigenemia is very strong predictor of disease progression.

SYNCITIUM INDUCING PHENOTYPE

Some of the HIV isolates who have syncitium inducing capacity are seen in later course of the disease.

CD38 POSITIVE CD8 T CELLS

The increased percentage of CD38 positive CD8 T cells reflects a high viral load which indicates the disease severity.

HIV RNA DETERMINATION

Plasma RNA is measured by RT – PCR , branched DNA assay or nucleic acid sequence based amplification. These assays can even detect a very low viral levels of 20 to 50 molecules. One of the indication for starting ART is plasma viral load of more than 30,000 copies/ml by bDNA assay and more than 55,000 copies/ml by RT PCR. Every 3 to 4 months of viral load monitoring is necessary after starting ART.

MONITORING CD4 T LYMPHOCYTE COUNT

Progressive CD4 depletion is hall mark of HIV disease. Lower levels of CD4 indicates severity and serious immunodeficiency .various methods for counting CD4 T lymphocytes are flow cytometry and dedicated cytometry. The gold standard is flow cytometry.

TERMINOLOGY OF UNTREATED HIV DISEASE

PROGRESSIVE GLA

The PGLA is a manifestations of early stage of HIV. It should be differentiated from other diseases causing lymphadenopathy such as infections and lymphomas.

AIDS RELATED COMPLEX

Now this terminology was abandoned. This is usually a manifestations of middle stage of HIV disease.

AIDS

This is the last stage, the centre for disease control and prevention published in September 1982 was revised once again to have additional conditions recognized as the late stage of HIV disease manifestations.

Table : 1 CDC CLASSIFICATION SYSTEM FOR HIV INFECTED ADULTS AND ADOLESCENTS:

CD4 CELL CATEGORIES	CLINICAL CATEGORIES		
	A ASYMPTOMATIC, ACUTE HIV, Or PGL	**B** SYMPTOMATIC CONDITIONS, NOT A or C	**C** AIDS-INDICATOR CONDITIONS
>=500 Cells/ microliter	**A1**	**B1**	**C1**
200-499 cells/ micro liter	**A2**	**B2**	**C2**
<200cells/ microliter	**A3**	**B3**	**C3**

In the above mentioned, category B symptomatic conditions are defined as that it should meet at least 1 of the following

1. They are attributed to HIV infection or indicate a defect in cell mediated immunity
2. They are considered to have a clinical course or management that is complicated by HIV infection.

Table : 2 WHO CLINICAL STAGING

Table 1: WHO clinical staging of HIV/AIDS for adults & adolescents 2010
Clinical Stage 1
Asymptomatic Persistent generalized lumphadenopathy
Clinical Stage 2
Unexplained moderate weight loss (<10% of presumed or measured body weight)' Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular Cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections
Clinical Stage 3
Unexplained 2 servere weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than one onth Unexplained persistent fever (above 37.5OC intermittent or constant for longer than one month) Persistent oral candidiais Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 109/litre) and or chronic thrombocytopenia (<50 x 109/litre3)
Clinical stage 4[3]
HIV wasting syndrome Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including menigitis Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis) Recurrent septicaemia (including non-typhoidal salmonella) Lymphoma (cerebral or B cell non Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or symptomatic HIV – associated cardiomyopathy

DIAGNOSIS OF HIV INFECTION

The standard screening test for the detection of HIV is by ELISA which has a sensitivity of more than 99.5%. But however the confirmatory test in the western blot which detects multiple antibodies to HIV proteins. Other tests are DNA PCR, RNA PCR, bDNA assay and P24 antigen capture assay.

GUIDELINES BY NACO FOR HIV DETECTION

STRATEGY I

This covers blood donor screening. A single ELISA is done, if it is found to be negative the donor serum is considered free of HIV, if it is positive it is not informed to donors.

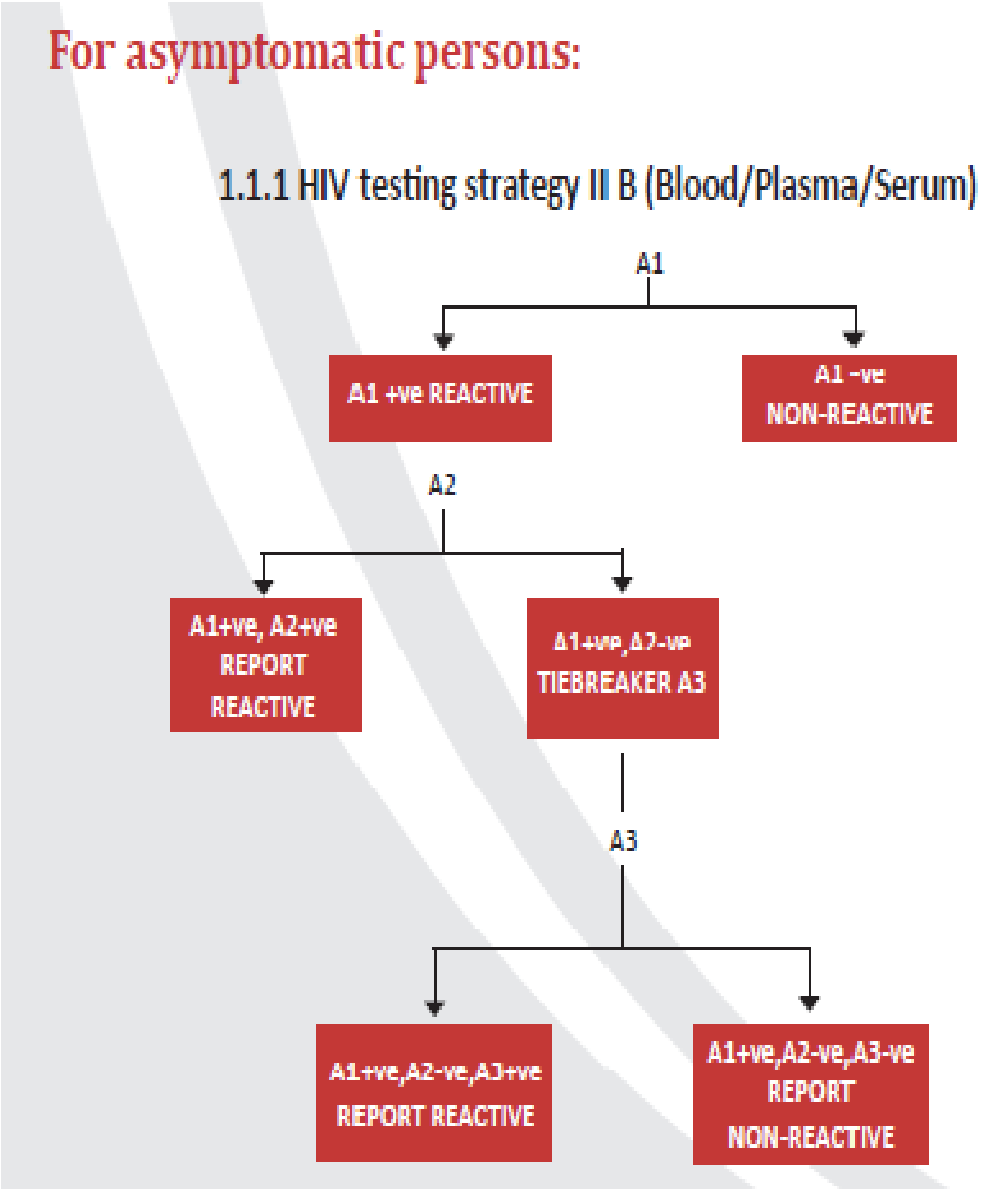
STRATEGY II

This is mainly for surveillance and diagnostic purposes. If the first ELISA is negative then the sample is considered negative, in contrast if the first sample is positive then the second ELISA is done and the test is reported as positive when both the tests are positive.

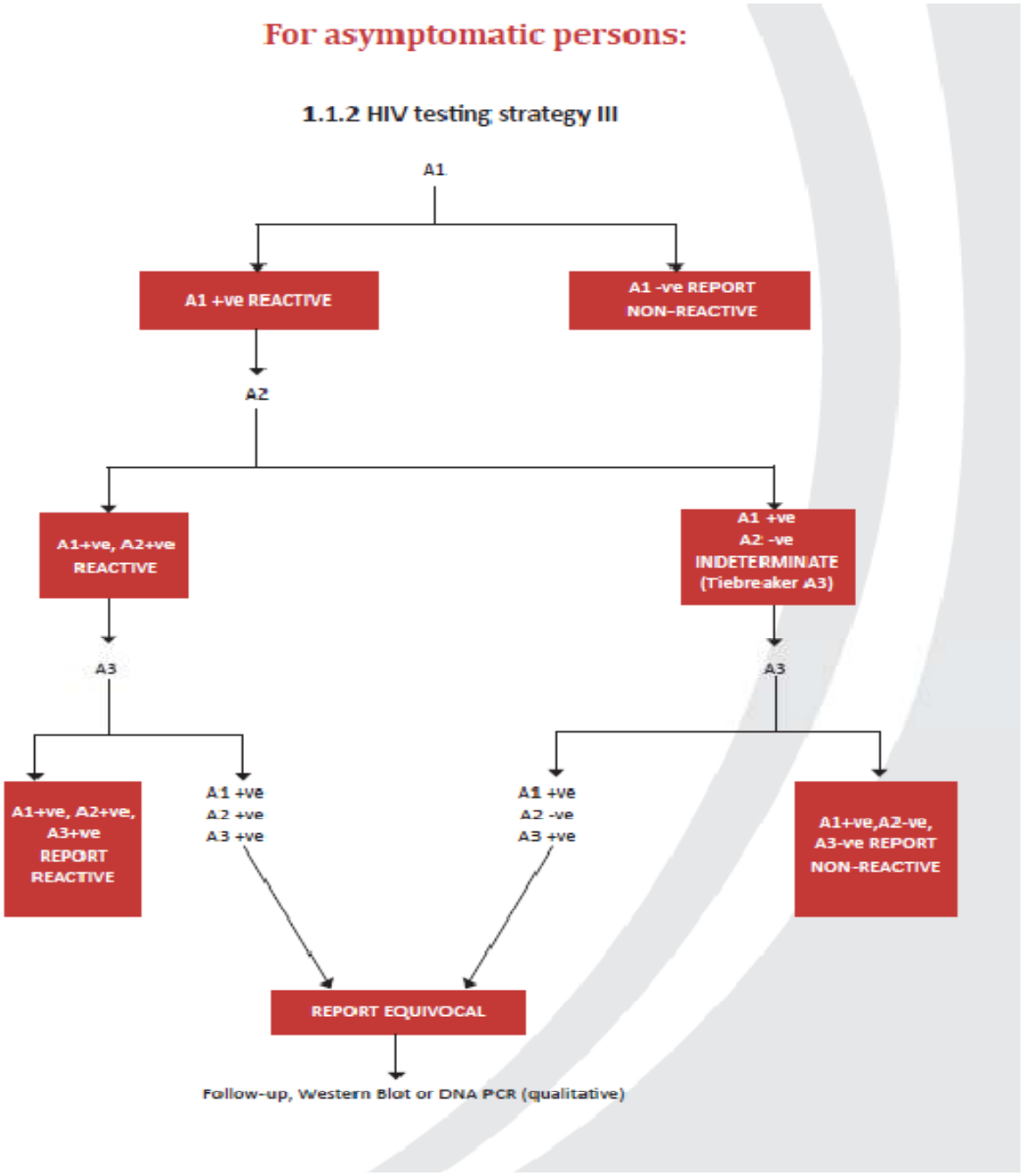
STRATEGY III

This is used to diagnose asymptomatic individuals. In this strategy a third reactive test is needed before reporting a positive result. For symptomatic persons the sample should be reactive with two different kits For asymptomatic persons the sample should be reactive with three different kits

STRATEGIES FOR ASYMPTOMATIC PERSONS



In practice a clinical/laboratory testing algorithm is required that employs more than one assay. This involves combination of two or more tests that use different testing principles, and which offer an increased combined sensitivity and specificity.



The tests should be definitely followed up by western blot or by DNA PCR if the report is considered as equivocal. After confirming with laboratory tests the iniation of ART begins

ANTIRETROVIRAL THERAPY

Indian government launched free ART program on 1st April 2004. There are about 18.13 lakh people living with HIV registered at 400 ART centers all over the country till march 2013. At present there are 6.5lakh people on 1st line ART. A greater decrease in deaths are noted in many states where significant scale up of ART services are achieved. With the current pace it is estimated around 50,000 to 60,000 deaths will be averted annually in next 5 years.

GOALS OF ART

- To improve the quality of life
- To reduce the HIV related morbidity and mortality
- To provide maximal and durable suppression of viral load
- To restore and (or) preserve immune function

Before starting the patients should be assessed clinically by

- Clinical Stage of HIV infection
- The patient's past illness
- Current HIV related illness
- Determine the need for ART and OIs prophylaxis.Find out other co-existing medical conditions and treatment that influence the choice of therapy

MECHANISM OF ANTIRETRO VIRAL THERAPHY

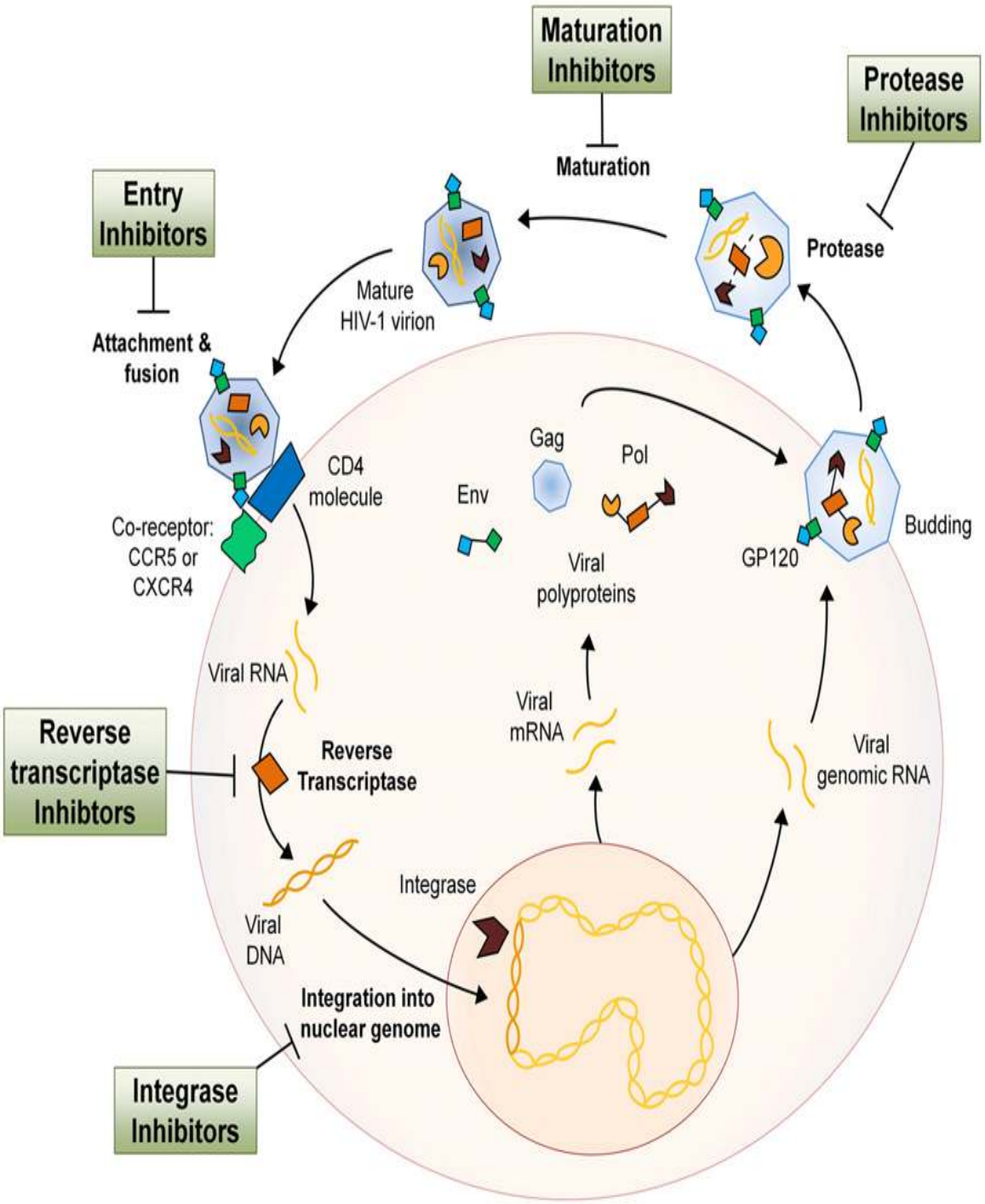


Table : 3 INDICATIONS FOR STARTING ART

WHO Clinical Stage	Recommendations
HIV infected Adults & Adolescents (Including pregnant women)	
Clinical Stage I and II	Start ART if CD4 < 350 cells/mm3
Clinical Stage III and IV	Start ART irrespective of CD4 count
For HIV and TB co-infected patients	
Patients with HIV and TB co-infection (Pulmonary/ Extra-Pulmonary)	Start ART irrespective of CD4 count and type of tuberculosis (Start ATT first, initiate ART as early as possible between 2 weeks to 2 months when TB treatment is tolerated)
For HIV and Hepatitis B and C co-infected patients	
HIV and HBV / HCV co-infection – without any evidence of chronic active Hepatitis	Start ART if CD4 < 350 cells/mm3
HIV and HBV / HCV co-infection – With documented evidence of chronic active Hepatitis	Start ART irrespective of CD4 count

The optimum time for the ART to be started is before the patient becomes unwell or presents with the first OI. The CD4 count should be assessed after stabilisation of any concurrent illness because the absolute CD4 count can vary with illness.

The patients should be started on ART as soon as possible when CD4 falls below 350. The CD4 count should be used as a supplement for determinig the stage of the disease. All HIV confirmed persons should be referred to ART centres for registration into care and screening for medical eligibility for ART by CD4 test and other baseline investigations. Don't delay ART initiation if the patient is clinically eligible according to the WHO clinical staging. CD4 monitoring is an important event for the HIV patients who are started with ART, so that it will enables the patients adherence, response to therapy.

Table : 4 FOLLOW UP SCHEDULE:

Table 6: CD4 monitoring and follow-up schedule	
CD4 Count	Follow up
CD4 of any value and on ART	Every 6 months
Between 350 and 500 and not on ART	Repeat at 3 months
>500 and not on ART	Repeat at 6 months
Note: If the CD4 count is between 350 to 400 cells/mm3 and the patient is not on ART; repeat CD4 assessment after 4 weeks and consider treatment in asymptomatic patients. *See Table 13 for more details p19.*	

Pre ART care is defined as the period where an HIV positive person does not medically require the initiation of ART. Patients who do not require ART should be counseled for a good healthy living habits and environment and should be linked with health providers and facility centres . Following steps are recommended for monitoring patients who are not eligible for ART.

1. Baseline screening of CD4.
2. Baseline lab assessment that includes CBC, ALT/AST, ALP, urinalysis.
3. Annual PAP smear screening for women
4. HBsAg and HCV screening for IDUs.
5. Any other relevant investigations and screening for TB at every visit.

Follow up visit for pre ART is very much important to assess the status of the patient.

Another important task in managing the pre ART patients are educating the patients. Since many of the patients once informed that their count is adequate not to be started on ART, they wont come properly for the follow up, so they must be informed to return back to ART centre once if they feels not well or any new symptoms develop such as difficulty in swallowing, severe unexplained fever, unexplained diarrhoea, severe cough with expectoration, hemoptysis, altered sensorium or seizures.

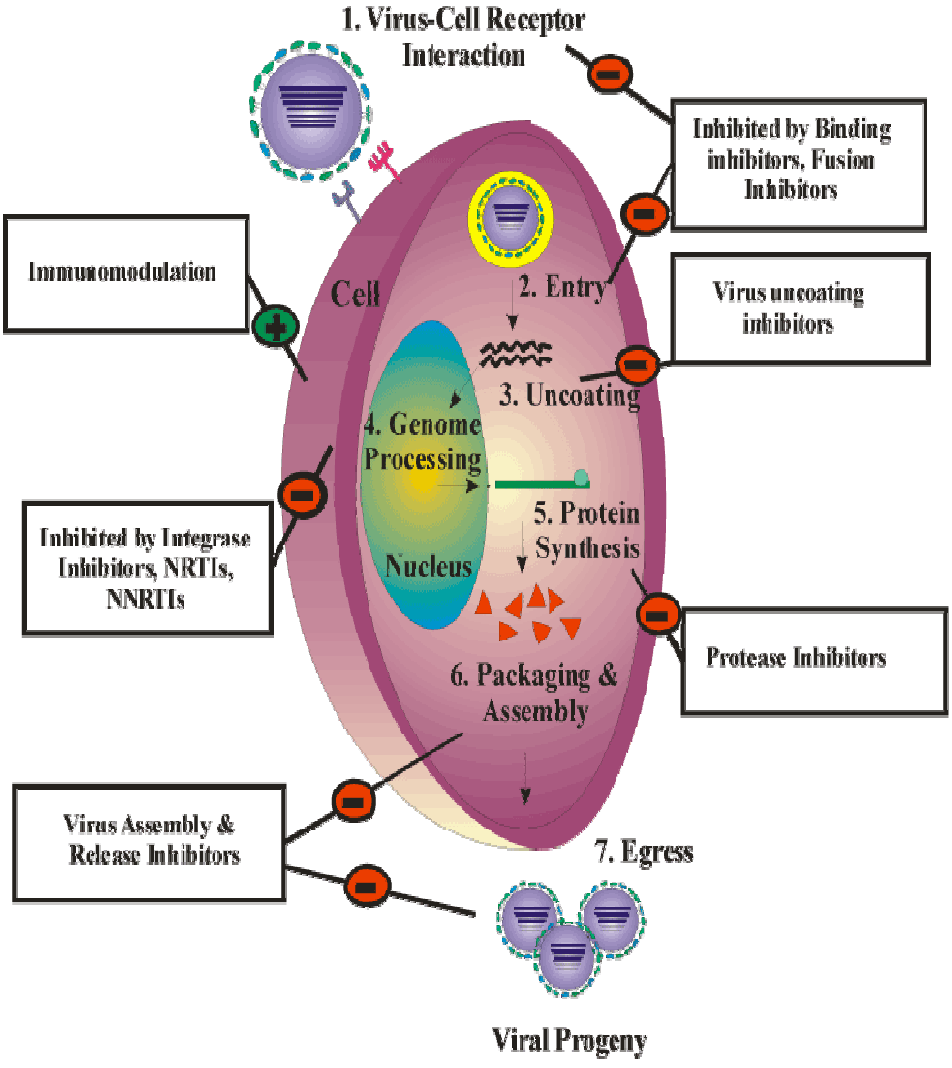
Table : 5 CURRENTLY AVAILABLE ANTIRETROVIRAL MEDICATIONS AND DRUG CLASSES

NRTI	NNRTI	PROTEASE INHIBITORS	INTEGRASE INHIBITORS	MATURATION INHIBITORS	FUSION INHIBITORS
Zidovudine	Nevirapine	Saqunavir	Raltegravir	Maroviroc	Enfuvirtide
Didanosine	Delavirdine	Ritonavir			
Stavudine	Efavirenz	Indinavir			
Lamivudine	Etravirine	Nelfinavir			
Abacavir		Lopinavir/ Ritonavir			
Tenofovir		Atazanavir			
Emtricitabine		Fosamprenavir			
Zalcitabine		Tipranavir			
		Darunavir			

NRTIs are analogues of naturally occurring deoxynucleotides, thymidine, adenosine, guanosine, cytosine and cytidine. All NRTIs are converted into triphosphate forms by intracellular phosphorylation. The main mechanism by which the NRTI inhibits viral replication is by due to its

lack of 3 hydroxyl group on the deoxyribose moiety, that prevents the further addition of nucleotides to the grouping DNA chain.

In contrast the NNRTIs inhibits binding to HIV reverse transcriptase, and competitively inhibits the enzyme and thereby prevents the normal movement of protein domain required for DNA synthesis.



GENERAL PRINCIPLES OF PHARMACOKINETICS AND PHARMACODYNAMICS

PHARMACOKINETICS

This process provides information related to the bioavailability of the drugs, the degree of protein binding, volume of distribution, elimination half life.

Gastric PH plays an important role in absorption of antiretroviral drugs particularly the protease inhibitors, the area under curve of which is decreased more than 75% in the presence of proton pump inhibitors, which should not be coadministerd. The volume of distribution is the relation between total amount of drug in the body and its concentration in the plasma. It is influenced by extent of plasma protein binding. Plasma protein binding is either to albumin or alpha-1-acid glycoprotein. Protein binding varies significantly with antiretrovirals with NNRTIs that are highly protein bound.

PHARMACODYNAMICS

It is the relation between drug concentration and the pharmacological response in terms of efficacy. The concentration of a drug should produce a effect without producing any toxicity and is termed as therapeutic range. It mainly deals upon the therapeutic effect, side effects, and toxicity.

BIOCHEMISTRY OF LIPOPROTEINS

The dietary fats and lipids synthesized from liver and adipose tissue should be transported to various tissues, due to its insolubility it should be transported by associating non polar lipids with amphipathic lipids and proteins.

The major composition of lipoproteins are lipids, proteis and a few amount of carbohydrates. Lipid content in lipoproteins are mainly of triacylglycerol, and phospholipids, cholesterol, cholesterylesters and some free fatty acids. The protein moiety of lipoproteins is called apolipoprotein. The major plasma lipoproteins are chylomicrons, very low density lipoproteins, intermediate density lipoproteins, low density lipoproteins and high density lipoproteins. They are disseminated among themselves by lipid content, density, size and proteins on their surface. Usually the chylomicrons and VLDL are not considered to be atherogenic

but the remnants of both of them namely chylomicron remnants and IDL are believed to be atherogenic. In liver cholesterol is excreted into bile, either directly or indirectly or after conversion into bileacids. Also it is transported from the periphery to the liver by the process called reverse cholesterol transport.

Another lipoprotein called Nascent high density lipoprotein are mainly secreted by the intestines and the liver and they will go for a modification which will becomes HDL2 and HDL3. They also play a very important role in cholesterol transport back into the liver. Many studies also find that triiodothyronine and insulin will increase the binding of LDL.

Table : 6 CLASSIFICATION OF LIPOPROTEINS:

Lipoproteins	Major Core Lipids	Apoproteins	Size
Chylomicrons	Dietary triacylglycerols, cholesterol esters	B-48, C, E	75-1200 nm
VLDL	Endogenous triacylglycerols	B-100, C, E	30-80 nm
IDL	Endogenous cholesterol esters	B-100, E	25-35 nm
LDL	Endogenous cholesterol esters	B-100	18-25 nm
HDL	Endogenous cholesterol esters	A, C, E	8-12 nm

Table : 7 CLASSIFICATION OF APOLIPOPROTEINS:

APOLIPOPROTEINS	LIPOPROTEINS	Mol. Mass (Dalton)	METABOLIC FUNCTIONS
apo AI	HDL, Chylomicrons	28,000	Structural component of HDL, LCAT activator
apo AII	HDL, Chylomicrons	17,000	Unknown; facilitates transfer of other apos
apo B48	Chylomicrons, Chylomicron remanents	2,60,000	It assembles the chylomicrons from the small intestine
apo B100	VLDL, IDL, LDL	5,50,000	It assembles and secretes VLDL from the liver
Apo CI	Chylomicrons, VLDL, HDL	7,600	VLDL receptor and liver uptake of chylomicrons are inhibited

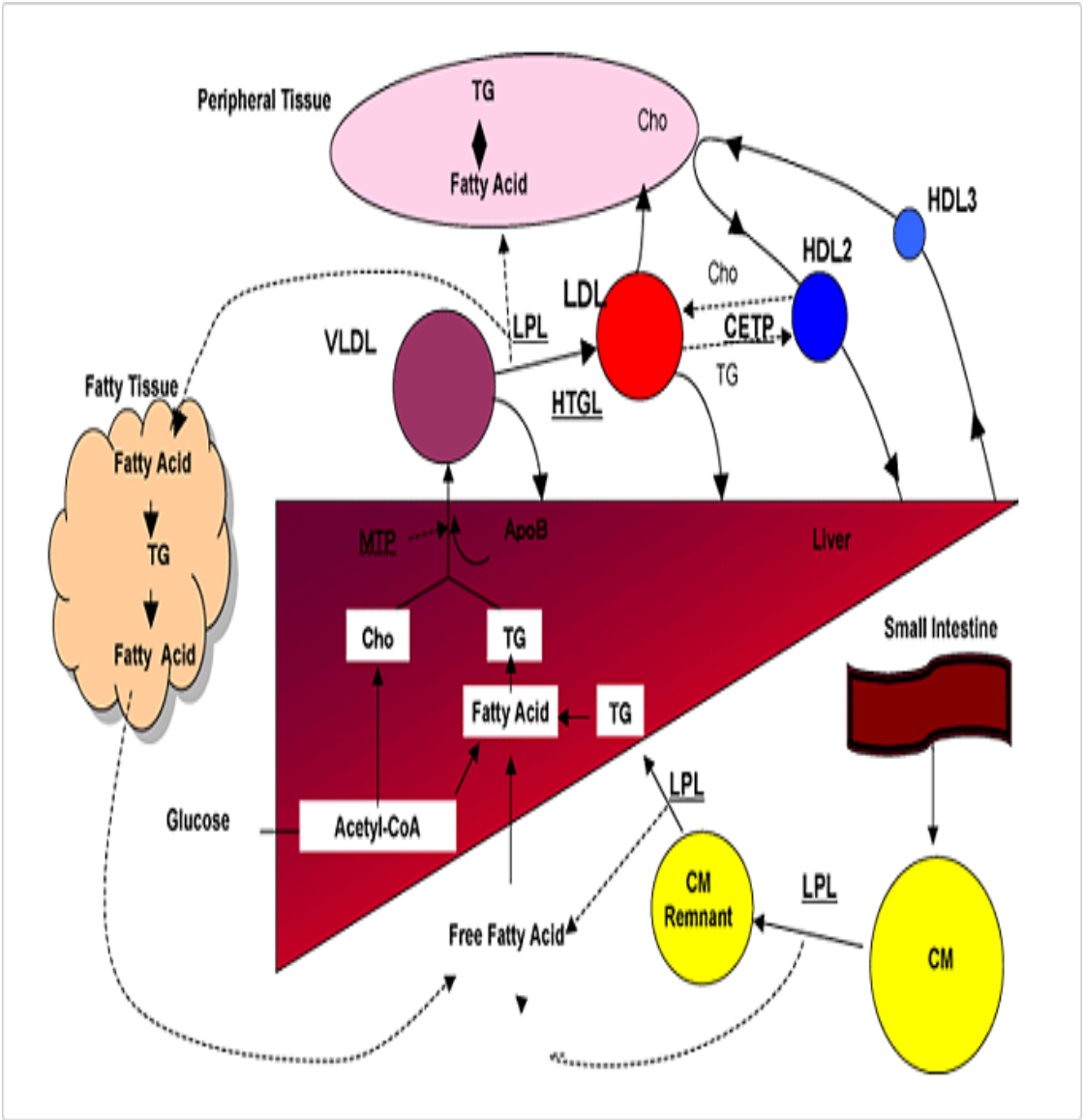
TRANSPORT OF EXOGENOUS LIPOPROTEINS

Normally the individuals with no dyslipidemia will dispose the dietary fat into the blood within 8 hrs, but the individuals who have dyslipidemia and especially those having increased fasting VLDL will have intestinally derived lipoproteins upto 24 hrs after the meal taken lastly.

In the human intestine the triglycerides and cholesterols taken by the diet are incorporated into chylomicrons. The content of chylomicrons are mainly by phospholipids, free cholesterol, apoB 48, apoAI, apoAII and apoAIV. Then the chylomicrons are transported through the thoracic duct into the circulation. ApoC proteins are transferred from HDL to the chylomicrons in the plasma, in capillary endothelial cells of fat and muscle, the triglycerides are hydrolysed by lipoproteinlipase which requires apoCII, where as the modulation of triglycerides hydrolysis is done by apoCIII. As a result of all above mentioned sequences the dietary triglycerides are transported to muscle and adipocytes as fatty acids and liver takes up the cholesterol from the diet where it uses it for bile acid formation and resecreted into circulation as lipoprotein cholesterol or into the bile.

Any abnormality that happens in transport or metabolism of chylomicrons will result in atherosclerosis. The main mechanism by which the delivery of cholesterol to the artery takes place is by the delay in their removal from plasma and elevated chylomicrons and their remnants postprandially.

TRANSPORT OF EXOGENOUS LIPOPROTEINS



TRANSPORT OF ENDOGENOUS LIPIDS

This includes transport of lipids from the liver to peripheral tissues and viceversa. Triglycerides are formed from fattyacids in the liver which are picked up from plasma or by denova synthesis from liver. The liver can also synthesise cholesterol. Then these lipids are made together with both phospholipids and apoB100 into VLDL and are secreted into the plasma.

The size of the VLDL is determined mainly by triglycerides. In conditions like calorie excess, diabetis mellitus, alcoholic consumption a very large triglyceride rich VLDL is secreted.

Even though the principal hepatic lipoproteins is VLDL in most individuals, both VLDL and cholesteryl enriched IDL can be secreted by liver in conditions with combined hyperlipidemia. LDL is formed mainly from smaller and more dense VLDL. The only protein which remains on the surface of LDL particle is apoB100.

The main determinant of half life of LDL in plasma is by LDL receptors(apoB100, apoE) availability. Liver takes up the most of plasma LDL and the remaining ones are transported to peripheral tissues that includes adrenals and gonads where steroid harmone synthesis takes place. The highest concentration of LDL receptors in our body is seen in adrenals. Goldstein and Brown are the forerunner who charecterised the LDL receptors role in cholesterol metabolism. The two main risk factors for atherosclerosis are increased plasma LDL and apoB100. On incubation with cultured macrophages or smooth muscles the normal LDL will not cause foam cell formation, but on lipid peroxidation it becomes a ligand, scavenger receptor pathway. The endothelial cells and macrophages that have scavenger receptors will cause uptake of modified lipoproteins which results in cholesterol laden foam cell formation. In addition it stimulates the secretion of cytokines and growth factors by various cells that synthesise and secrete collagen.

In atherogenesis the role of VLDL is uncertain. The main reason is due to inverse relation between decreased level of HDL and increased level of triglycerides and is of possible which hypertriglyceridemia may not cause direct atherogenesis but the surrogate markers can cause. Also the cholesteryl esters enriched with VLDL will cause foam cell formation. The main determinant of risk of atherosclerosis from elevated

VLDL and hypertriglyceridemia is by the level of cholesteryl esters enriched VLDL remnants. The atherogenic potential of IDL and VLDL remnants are the same.

ASSOCIATION BETWEEN LIPOPROTEINS AND ATHEROSCLEROTIC HEART DISEASE

HYPERCHOLESTEROLEMIA

The main factor that is clearly associated with increased risk of CAD is hypercholesterolemia. 70% of the cholesterol is found in LDL which is the primary target for intervention in the guidelines under NCEP.

LDL

Low density lipoproteins also influences the CAD risk. LDL occurs in conjunction with increased TGL ,low HDL , truncal obesity, and hypertension. The exact mechanism by which LDL causes atherogenesis is still unclear. In comparision with large LDL, the scialic acid content of small LDL is low which may cause increased binding capacity of LDL to proteoglycans in the arterial wall. When the density of LDL particles are increased it is found that there is dose dependant increase in thromboxane synthesis. Also small LDL are more vulnerable to invitro oxidation when compared to large LDL. It has been evidenced

that by lowering the LDL-C there is reduction in cardiovascular mortality.

OXIDISED LDL

Due to the exposure to the endothelial cells, smooth muscle cells, macrophages the LDL gets oxidized. Due to this oxidation it attracts monocytes which is adhered to the arterial wall, and is prevented from dissociation with arterial wall scavenger receptors and so intracellular cholesterol accumulates. Due to the continuing uptake the macrophages are converted into lipid laden foam cells, which is the main culprit of atherosclerotic lesion.

TRIGLYCERIDES

TG s are independent risk factor for coronary artery disease, so the remnant lipoproteins (mixture of TG s and some lipoproteins) should be atherogenic. There is definite correlation between CAD and TG s. Triglycerides being atherogenic it causes various complications that are life threatening. Females have a definite risk factor for CAD with increased TG s. Above 65 years [1] TG s are considered to be an important predictors of CAD. Many studies also suggested that in patients with type 2 DM there is definite positive association between CAD and number of triglycerides in plasma.

HDL

HDL possess an inverse relationship with atherosclerotic cardiovascular disease. Also HDL is an antioxidant to LDL-C has it decreases the platelet aggregation. So that it is always mentioned as good cholesterol. As we all know HDL transports cholesterol from peripheral tissues to liver by the process termed reverse cholesterol transport, which reduces the oxidation modification of LDL, thereby it acts on endothelial cells and cytokine induced expression of adhesion molecules. A study on adenosinetriphosphate binding cassette(ATPC) proteinA1 transporter have finded a role of this transporter in liver and peripheral tissue [2] with the levels of HDL and cholesterol. It is also founded that the persons with cardiovascular diseases has low levels of HDL-C [3].

METABOLIC COMPLICATIONS OF HIV

Insulin resistance, dyslipidemia , lipodystrophy, are commonly seen in adults with HIV infection and also is more pronounced in patients receiving HAART [4]. These complications will increase the patients risk for cardiovascular complications and thereby increases the mortality, because of these metabolic complications the quality of life is very much questionable among them.

DYSLIPIDEMIA IN HIV PATIENTS ON HAART

The association of dyslipidemia in the patients already started on HAART is of a different pattern from patient going to be started on HAART. Mainly protease inhibitors and some of the non nucleoside reverse transcriptase inhibitors have been found to alter the lipid profile in such a manner to be complicated with cardiovascular complications. It has been found that there is increase in total cholesterol, triglycerides, LDL-C, lipoprotein a[5]. Protease inhibitors and some of the NNRTIs inhibits a protein called sterol regulatory enhanced binding protein-1 (SREBP I) which causes a increased lipid production by the liver [6]. The other important factors that causes dyslipidemia are visceral fat accumulation, lipoatrophy, insulin resistance.

The main mechanism by which the NNRTI s induces lipoatrophy is by inhibition of SREBP1 that mediates activation of retinoid x receptor PPARY coactivator 1 [7].

An important cross sectional study conducted by Friis moller et al reported that about 23% of patients who receives a NNRTI and 10% who receives only NRTI has elevated levels of cholesterol of about more than 240 mgs when compared to only 8% of previously untreated patients. The same data for that of triglycerides of more than 200 mgs are 32% and 23% on comparision with only 15% among patients of previous subjects

who have not yet started on ART, this makes a definite difference of dyslipidemia induced by HAART.

Also low levels of HDL of about less than 35 mgs were reported with 19 and 25% of subjects on treatment when compared to 26% those have not started on ART. Framingham offspring cohort study found that some evidence for body fat abnormalities that 57% of individuals has elevated TG s more than 200 mgs and 46% of individuals with HDL of less than 35mg.

There was a prevalence rate of 57% among patients infected with HIV for cholesterol above 200 mg when compared to controls in Framingham study which is 42%.

By inhibition of mitochondrial DNA polymerase of adipocytes the nucleoside analogues cause lipoatrophy and dyslipidemia through mitochondrial injury. Efavirenz based regimens have been found to cause more dyslipidemias and cardiovascular risk factors when compared to nevirapine based regimens. The two mechanisms by which those drugs cause insulin resistance and hepatic steatosis are impaired fatty acid oxidation which causes intra myocellular fat accumulation, and increased circulating fatty acids.

FAT ABNORMALITIES IN HUMAN BODY

It has been reported that about 40 to 50% of HIV infected patients have abnormalities in body fat composition and the above mentioned proportion is in higher level in patients receiving HAART [8, 9 ,10]. There is wide variability in prevalence rates from 11 to 83% as mention in many cross sectional studies [11, 12].

Depending upon the charecteristics (age, sex, race) , type and duration of HAART and the population that we are comparing, the lipodystrophy rates may vary [13]. There is no clear cut evidence of differentiation in definitions of loss of subcutaneous fat and gain in truncal fat. A study based on DEXA that is dual energy X ray absorptiometry and CT was validated but still it is not recommended in our clinilal practice.

There is subcutaneous lipoatrophy and accumulation of fat in HIV patients. Subcutaneous lipoatrophy is mainly noted in face, limbs buttocks and trunk [13]. Visceral fat is mostly accumulated as central fat. There is variation in total abdominal fat accumulation and also it is independent of peripheral fat loss. The area that fat accumulates are breast, over dorso cervical spine, muscle and the liver. This pattern of fat distribution that is central lipohypertrophy will results in increased waist hip ratio (WHR).

Prospective studies that investigates total body fat composition in those who are going to be started on ART first time have found to have initial increase in fat in limbs during their first few months, which is then followed by progressive decline during the upcoming three years [14]. But in contrast there is increase in truncal fat initially followed that there is a stable phase in ensuring two or three years that results in central adiposity. There are clinical evidence of changes in central and limb fat masses in about 20 to 35 % patients after starting HAART [14 15].

PATHOGENESIS OF LIPODYSTROPHY

There is a change in body fat composition in patients who have not received HAART but it has been observed that maximum changes will occur after starting HAART.

It also been founded that the syndrome is less likely to be caused by direct effect of HIV. It is exclusive to those who received HAART. Also there is improvement in both lipoatrophy and visceral fat accumulation after reverse transcriptor switch over without any changes in viral load [16]. Also many studies have found that there is no or negative association between increasing HIV RNA and lipodystrophy.

The strong association with severity of lipoatrophy is mainly by type, duration and use or nonuse of HAART particularly in a combination

between two NRTI and a PI s which both of them have a strong association with lipoatrophy [17]. So that these main two ARTS are concerned with cardiovascular complications and thereby increases the morbidity and mortality.

NNRTIs will induce lipoatrophy by inhibiting SREBP1 mediated activation of adipocyte retinoid x receptor and peroxisome proliferators activared receptor gamma (PPAR gamma) or by PPAR gamma coactivators 1 [18, 19].

The nucleoside analogue that is strongly associated with lipoatrophy is stavudine especially when used with didanosine [20, 21]. The mechanism by which the nucleoside analogues causes lipoatrophy is due to mitochondrial injury that results from inhibition of mitochondrial polymerase gamma within the adipocytes [22], and also by depletion of mitochondrial DNA [23]. Also the nucleoside analogues will inhibit the adipogenesis and adipocyte differentiation [24]. The factors that are associated with lipoatrophy are old age, lower body weight, prior to the diagnosis of AIDS and a lower CD4 count. Womens have more central fat accumulation than men [25]. Increased fatty acid storage and impaired fatty acid oxidation or both of them will result in increased intracellular lipid contents, hepatic steatosis and insulin resistance [26, 27, 28].

Generalised wasting will occur in HIV other than lipodystrophy. An AIDS defining condition is generalized wasting. It is defined as more than 10% involuntary weight loss in association with intermittent or constant fever, fatiguability and chronic diarrrhoea that lasts for more than 30 days in the absence of a defined cause other than HIV infection. The most consistent feature of this syndrome is severe muscle wasting with myofibre degeneration and occasionally myositis [29].

INSULIN RESISTANCE AND ABNORMAL GLUCOSE HOMEOSTASIS

A surrogate marker for insulin resistance that is hyperinsulinemia is most commonly seen in patients having increased truncal fat, decreased fat in limbs, increased waist hip ratio, and a buffalo hump [30]. As by Carr et al [31] who matched for age and body mass index with that of HIV infected individuals having lipoatrophy or fat accumulation the diabetes mellitus was seen in 7 % of individuals when compared with healthy controls. Also the impaired glucose tolerance was seen in 35% of HIV infected subjects in comparison with just only 5% with healthy controls. In some other longitudinal study it was observed that the development of diabetes mellitus in HIV patients receiving combination HAART over a 3 year period of observation was found to be 3.1 times when compared to

those who are not receiving. The rate at which both the above mentioned categories that progress to overt diabetes is not known.

PATHOGENESIS

ART will leads to increased free fatty acid production, intramyocellular fat accumulation, adipokine level alteration and a decreased PPAR gamma expression with a altered glucose homeostasis[32]. Various ART s also found to cause insulin resistance invitro by decreasing the glucose transport which was mediated by GLUT 4 transporter[33]. Insulin sensitivity is affected by change in body composition[34, 35]. Nucleoside analogues will cause insulin resistance through changes in fat distribution.

CLINICAL CONSEQUENCES

As we already seen that the metabolic complications such as dyslipidemia, insulin resistance, loss of subcutaneous fat and increase in central fat are commonly seen in patients infected with HIV. These complications increase the risk of both cardio and cerebrovascular complications. The other main risk associated with increased TG levels is pancreatitis. The pancreatitis which results from the effect of triglyceridemia will result in acute abdomen, vomiting, faintness, severe dehydration, and can lead to death.

CARDIOVASCULAR DISEASE

After the introduction of protease inhibitors and non nucleoside reverse transcriptase inhibitors for HIV infection, it was observed to have many unexpected cardiovascular complications with the patients receiving ART, eventhough the patient undergoes many and many complications induced by the disease itself, in addition the drugs induced for cessation of disease progression may also induces several complications. The young people receiving this HAART also can met with angina, MI, stroke and also sometimes peripheral vascular disease. There is also confusion among clinicians that these complications are either due to chronic HIV infection itself or due to new anti HIV regimens.

Another study conducted from Kaiser permanente medical care programme from northern California founded that the HIV patients regardless of the use of HAART therapy was hospitalized for cardiovascular and cerebrovascular complications of about 1.5 times than that of uninfected counterparts [36].

Another data was collected from more than 24,400 patients from Europe, United states and Australia conducted by Friis moller and collaborators on adverse effects of HAART. From this study it was found that over a median period of 1.6 years about 126 patients had

myocardial infarction. Also on analyzing the duration of drug exposure they came to know that in the first 4 to 6 years of combination therapy, there was about 16% relative increase in rate of MI per year.

DAD study group reported about 346 deaths that are due to cardiovascular events with a confirmed incidence of 3.45% in comparision to 1.4% in controls. There is inevitable increase in risk of cardiovascular disease among HIV patients due to their pre existing burdens of traditional risk factors such as old age, smoking, hypercholesterolemia, DM, male sex, previous history of MI [37]. Not all but some of cardiovascular risks may be due to effect of HIV infection or due to ART or due to combined effect of all of them, whatever may be the effect, the patient are caught hold of numerous complications that are especially dealt with the cardiovascular system.

MECHANISM

Like other infectious agents such as cytomegalovirus, herpes simplex, and Chlamydia, HIV infection itself will cause atherosclerosis on endothelial cells through proinflammatory effect, that causes various complications. It causes cardiovascular instability either directly or due to various drugs. On getting HIV infection there is reduction in HDL cholesterol level.

The disease progression and HIV viremia is strongly associated with hypertriglyceridemia [38]. When compared to uninfected controls the infected persons at the median age of 45 years it is noted that there is increased carotid intimal thickness and increased rate of disease progression. The risk factors such as hypertension, hypercholesterolemia, smoking, diabetis mellitus, alcoholism, are strongly associated increased carotid intimal thickness. In electron beam computed tomography, it is found to have coronary artery calcifications in HIV patients, the fibrinolysis is impaired in HIV patients in terms of increased tissue plasminogen activator and plasminogen activator inhibitor 1.

The ART will further increase atherosclerosis either directly or indirectly. The two main mechanisms are endothelial dysfunction and decreased flow mediated dilatation seen in patients receiving protease inhibitors [39]. The patients receiving ART have increased risk of developing hypertension than who have not, also it is associated with increased body mass index. The main aim is to detect the metabolic abnormalities attributed by ARTs which indirectly causes atherosclerosis. Another important mechanism is by increasing the CD 36 dependant cholesterol ester in macrophages the protease inhibitors will promote atherosclerosis [40].

In addition some ARTs are associated with insulin resistance. Patients on ARTs have lipodistrophy which will itself causes atherosclerosis, so the HIV treated patients will have lipodystrophy, diabetes, elevated lipoproteins which have the toxic effects on endothelium. So in nutshell the patients started on ART have a greater risk of development of atherosclerosis.

The exact mechanism of vascular events in HIV infected patients are not clearly known, but may be related to DM, dyslipidemia, insulin resistance, inflammation, impaired fibrinolysys, factor related to ARTs or combination of above factors.

ASSOCIATION WITH PANCREATITS

The increased triglycerides levels seen in HIV patients or patients receiving HAART has found to have serious pancreatitis but this is not reported in literature.

METABOLIC AND BODY FAT ABNORMALITIES

ASSESSMENT

DYSLIPIDEMIA

In every HIV patients fasting lipid profile have to be measured before initiating ART and also after changing ART regimen , in addition the family history of dyslipidemia, DM, alcohol intake, or any other

medications intake is to be determined**.** The possible ART which worsens the lipid levels should selected for patients with dyslipidemia.

GLUCOSE HOMEOSTATIC ABNORMALITY

Fasting glucose levels should be measured before starting ART and should be then measured annually, as well as when there is a change in ART. Weight and any family history of diabetes also should be assessed. There will be definite impaired glucose tolerance and insulin resistance in those patients before the development of overt diabetes.

Hyperinsulinemia and impaired glucose tolerance are the two major risk factors for cardiovascular complications. So a fasting glucose or oral GTT should be performed in patients with HIV started on ART.

ABNORMALITIES IN BODY FAT

It should be mandatory to have annual assessment of body fat for the patients to be started on HAART, especially on protease inhibitors or NRTIs or NNRTIs as well as to patients who are going to be switched over to other ARTs. Dual energy Xray absorptiometry is used for measuring fat in the limbs. Also the additional information are provided by measuring the truncal and limb fat, WHR measurement, thigh circumference. CT scan gives us extra information about visceral and abdominal fat. Due to the risk of radiation exposure it should not be used

clinically. For assessing facial lipoatrophy no techniques has been validated.

MODIFICATION OF RISK FACTORS

All risk factors that includes dyslipidemia, insulin resistance, hypertension, smoking, alcohol intake, sedentary life style, family history should be assessed carefully. The first recommendation that includes are lifestyle modification and dietary alterations, interventions for smoking and hypertension, subsequently the lipid lowering therapies or a change in ART should be considered. The measures for DM and insulin resistance includes initiation of insulin sensitizing agents. The modification should be in such a manner that it should balance both the risk of cardiovascular events and risk of progression of HIV disease to that of long term use of retroviral therapy , eventhough there is increased risk of cardiovascular disease in HIV patients, it is almost low to outweigh the benefits from aministering ARTs. For the patients with advanced disease or HIV patients who are resistant to ART the risk of cardiovascular complications are a lesser concern. So when we are planning to initiate ART it should be kept in mind that the ART which we are going to start should have a lower propensity to elevate lipid or glucose levels.

ANTILIPEDEMIC DRUGS

To treat isolated hypercholesterolemia statins are used and for isolated hypertriglyceredemia fibrates are used. Both the statins and fibrates can also be tried if the response is incomplete provided there should be careful monitoring of creatine kinase and aminotransferase levels [41, 42, 43]. Usually the guidelines provided by NCEP should be followed when initiating lipid lowering therapy in HIV infected patients until other specific recommendations are available. Drug interactions between lipid lowering agents and ARTs should be always kept in mind[44].

INSULIN SENSITISORS

Metformin which is a insulin sensitisor have been found to improve insulin sensitivity and decrease the visceral adiposity, reduces tissue plasminogen activator and plasminogen activator inhiobitor 1, and also the BP. Another molecule ROSIGLITAZONE is used in patients with insulin resistance.

GROWTH HORMONE

Usually the growth hormone levels are low in patients with HIV infection especially who have excess visceral adiposity and in those

patients growth hormone secretogogues can be tried to restore the body fat to normal back [45,46,47,48].

ROLE OF SURGERY

For facial lipoatrophy various injectable agents are tried. A reabsorbable molecule polylactic acid is used widely which promotes collagen formation and it improves facial soft tissue appearance. Liposuction can be tried on patients especially with dorsocervical fat.

SWITCHING OVER TO OTHER REGIMENS

Cessation of zidovudine can generally lead to improvement in limb fat. Replacement of drug for the other which has the low potential to increase the above mentioned complications can be tried [49,50,51,52]. However the cessation of drugs alone cannot improve the lipoatrophy.

MATERIALS AND METHODS

Setting: HIV patients of age from 18 to 60 years who were attending ART Centre, Coimbatore medical college hospital, and patients admitted in Medical and STD wards at CMCH- CBE.

Collaborating Department: Antiretroviral therapy centre, CMCH – CBE, Biochemistry department, CMCH

Design of study	:	Observational study.
Period of study	:	1 year.
Sample size	:	100
Ethical committee approval	:	obtained
Consent	:	informed consent obtained
Financial support	:	nil
Conflict of interest	:	nil

METHODOLOGY

STUDY DESIGN : observational study

PATIENT SELECTION : 100 diagnosed HIV patients in Coimbatore medical college hospital was selected and the study was conducted during the year 2013-14 which includes 50 patients started on HAART and 50 patients not started on HAART.

INCLUSION CRITERIA :

- HIV patients attending the ART centre
- Age group of both sexes 18 to 60 years
- Patient with good adherence to HAART

EXCLUSION CRITERIA :

- Diabetes
- Hypertension
- Coronary artery disease
- Chronic renal failure
- Already diagnosed dyslipidemic patients
- Obesity (BMI > 25)

TECHNIQUES :

HISTORY AND EXAMINATION :

Patients included in the study were divided into five groups

Group 1 : patients on ZDV+3TC+NVP (no of patients : 12)

Group 2 : patients on ZDV+3TC+EFV (no of patients : 14)

Group 3 : patients on TEN+3TC+NVP (no of patients : 6)

Group 4 : patients on TEN+3TC+EFV (no of patients : 18)

Group 5 : patients not started on HAART.

A proforma containing details for every patient that includes age, relevant history of smoking, alcoholism, marital status, history of TB. The height was measured barefoot in meters and weight in kilograms in a normal indoor clothing. Waist circumference was measured in terms of narrowest measurement in between ribcage and the iliac crest, vital signs were recorded and clinical examination of all the systems were made.

FASTING LIPID PROFILE MEASUREMENTS

The patients venous blood samples will be taken to measure the serum lipid profile levels with 12 hours overnight fasting for both the groups. Fasting lipid profile levels will be measured. Lipid profiles

will be repeated at 6 months and one year. The lipid profile estimation was done in ERBA – XL 300 automatic analyser.

STATISTICAL METHODS :

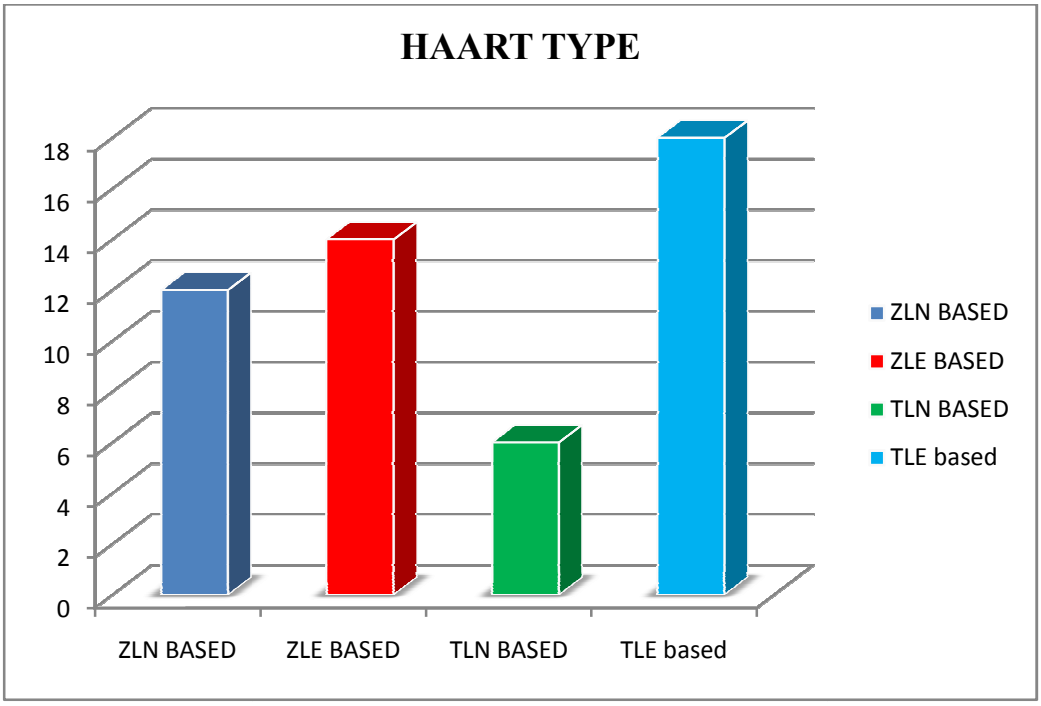
The Statistical analysis was performed using SPSS version 19.0 . Normal data was measured using mean and standard deviation . To correlate various clinical variables pearson correlation co-efficient with single tail analysis was done.

RESULTS

TABLE : 8 DISTRIBUTION ACCORDING TO REGIMEN

REGIMEN	HAART
ZLN	12
ZLE	14
TLN	6
TLE	18

CHART : 1 DISTRIBUTION ACCORDING TO REGIMEN



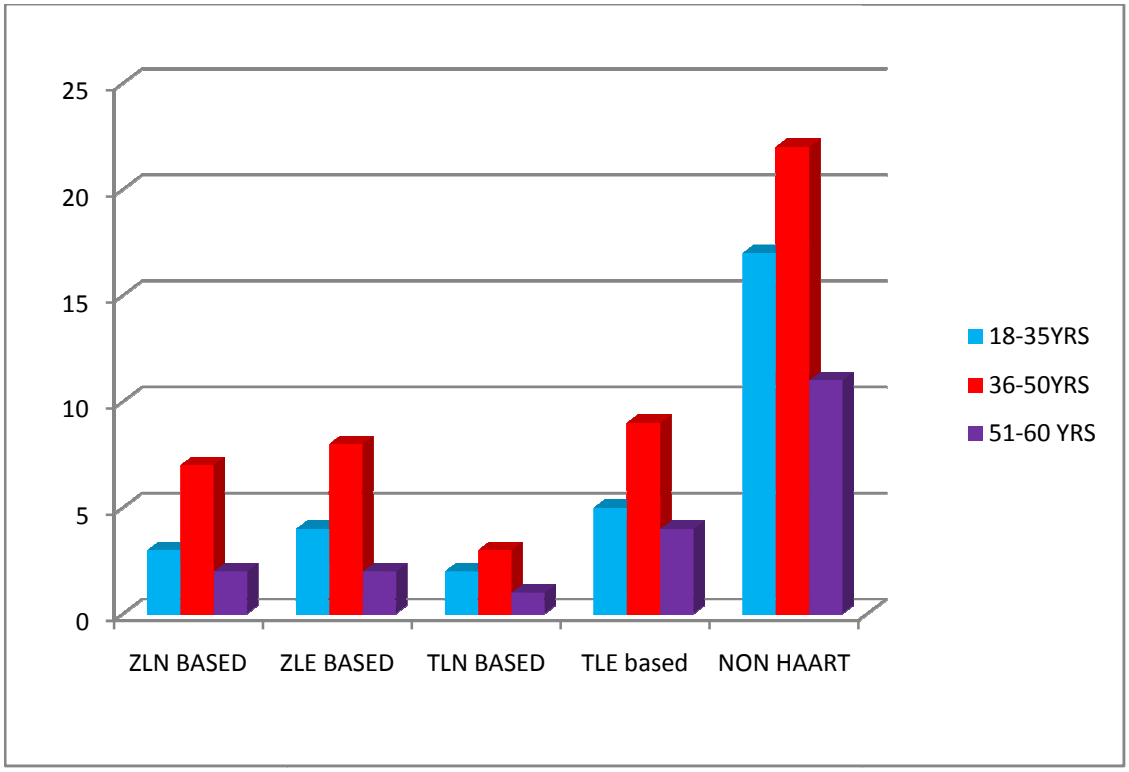
About 100 patients was selected in the study, they were divided into 5 groups. The first group was on ZDV+3TC+NVP, this group has about 12 members, the second group was on ZDV+3TC+EFV which has 14 members, then the third group on TEN+3TC+NVP with 6 members, the fourth group of TEN+3TC+EFV with 18 members, then the final fifth group of non HAART with 50 members. In the patients on HAART group maximum number of patients falls into group 4 which was on TEN+3TC+EFV with 36%, the least number of patients falls into group 3 those who are on TEN+3TC+NVP of about 12%.

In coimbatore medical college hospital we are using only first line regimen that includes Zidovudine, Lamivudine, Efavirenz, Nevirapine, Tenofovir.

TABLE :9 AGE WISE DISTRIBUTION

HAART	18-35YRS	36-50YRS	51-60YRS
ZLN	3	7	2
ZLE	4	8	2
TLN	2	3	1
TLE	5	9	4
NON HAART	17	22	11

CHART : 2 AGE WISE DISTRIBUTION

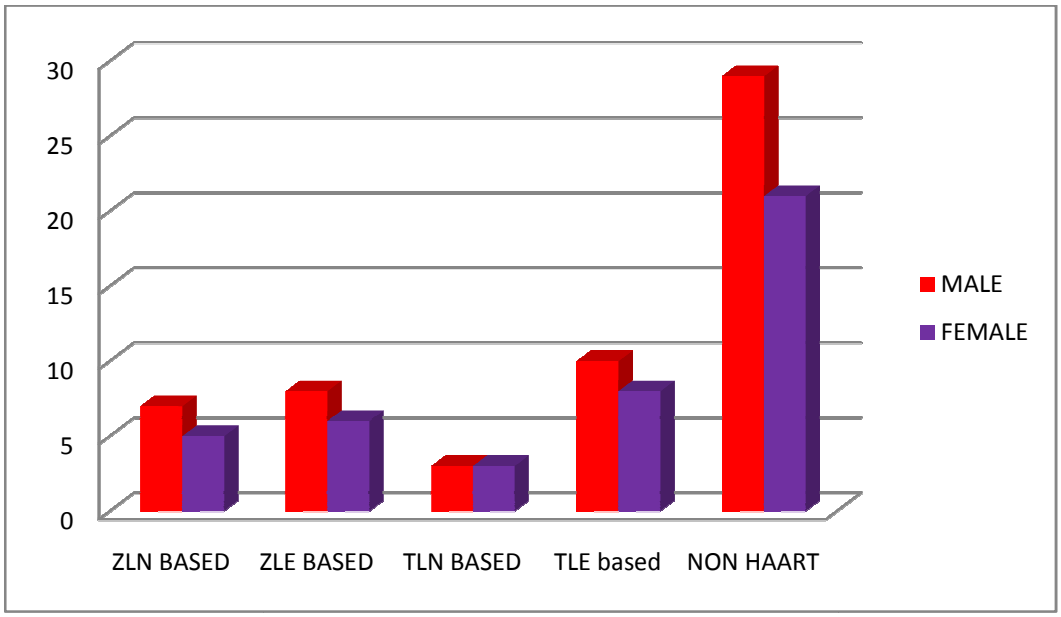


The age wise distribution among HAART patients at the age 18-35 are about 14, the patients in the age group between 36-50 are about 27 and in 51-60 are 9, the patients in non HAART are 18-35, 36-50,51-60 are 17,22,11 respectively.

TABLE : 10 SEX DISTRIBUTION

	MALE	FEMALE
ZLN	7	5
ZLE	8	6
TLN	3	3
TLE	10	8
NON HAART	29	21

CHART : 3 SEX DISTRIBUTION

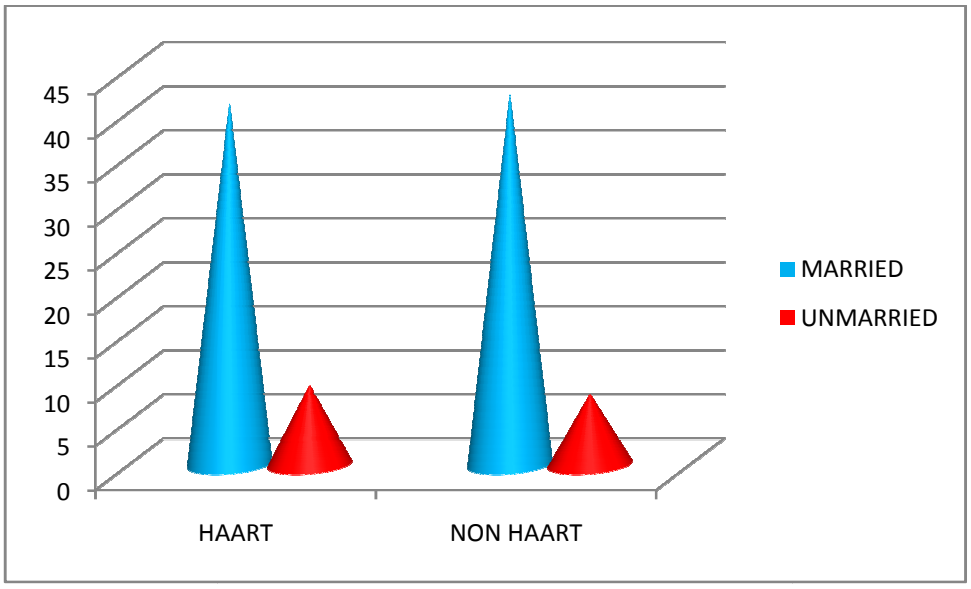


The number of males in the goup 1 to 4 are 7, 8, 3, 10 respectively and the number of females are 5, 6, 3, 8 respectively, the patients in the non HAART are about 29 males and 21 females.

TABLE : 11 MARITAL STATUS OF THE PATIENTS

	HAART	NON HAART
MARRIED	41	42
UN MARRIED	9	8

CHART : 4 MARITAL STATUS

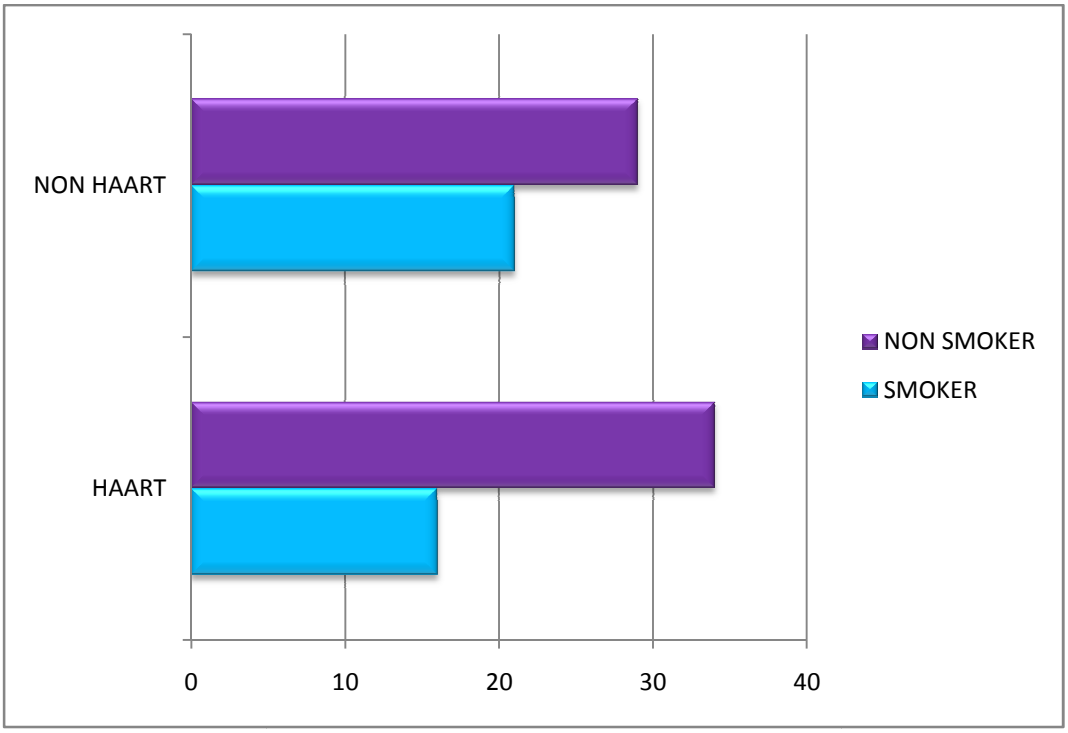


The number of patients in the HAART group those who are married are 41 and the unmarried patients are 9, the number of married patients in the non HAART are 42 and the unmarried patients are 8, with 82% , 18%,84%,16% respectively.

TABLE : 12 DISTRIBUTION BETWEEN SMOKERS AND NONSMOKERS

	HAART	NON HAART
SMOKER	16	21
NON SMOKER	34	29

CHART : 4

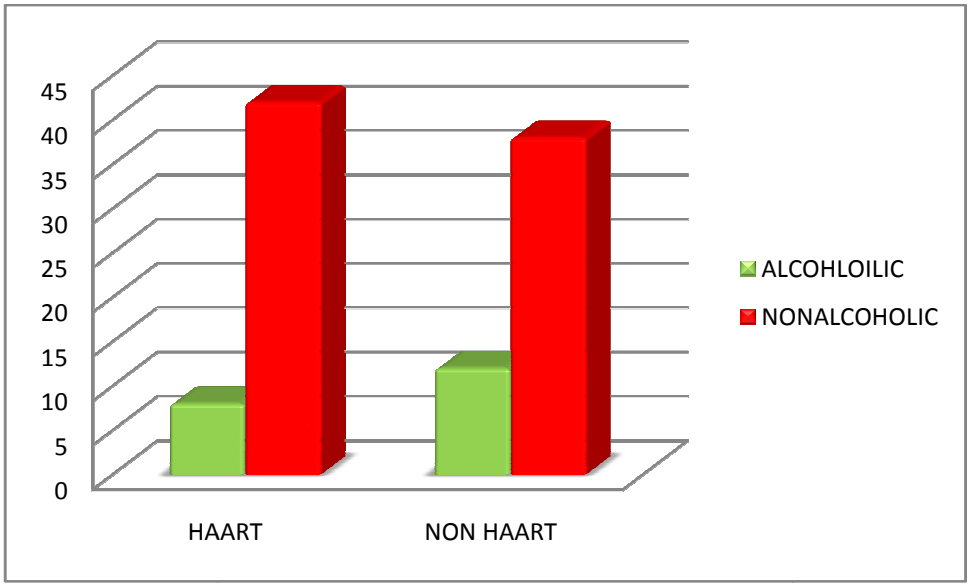


The patients who are smoking in HAART group are 16 with 32%, and the non smokers are 34 with 68%, the patients in the non HAART who are smoking are 21 with 42% and those who are not smoking are 29 with 58% .

TABLE : 13 DISTRIBUTION BETWEEN ALCOHOLICS AND NON ALCOHOLICS

	HAART	NON HAART
ALCOHOLIC	8	12
NON ALCOHOLIC	42	38

CHART : 5

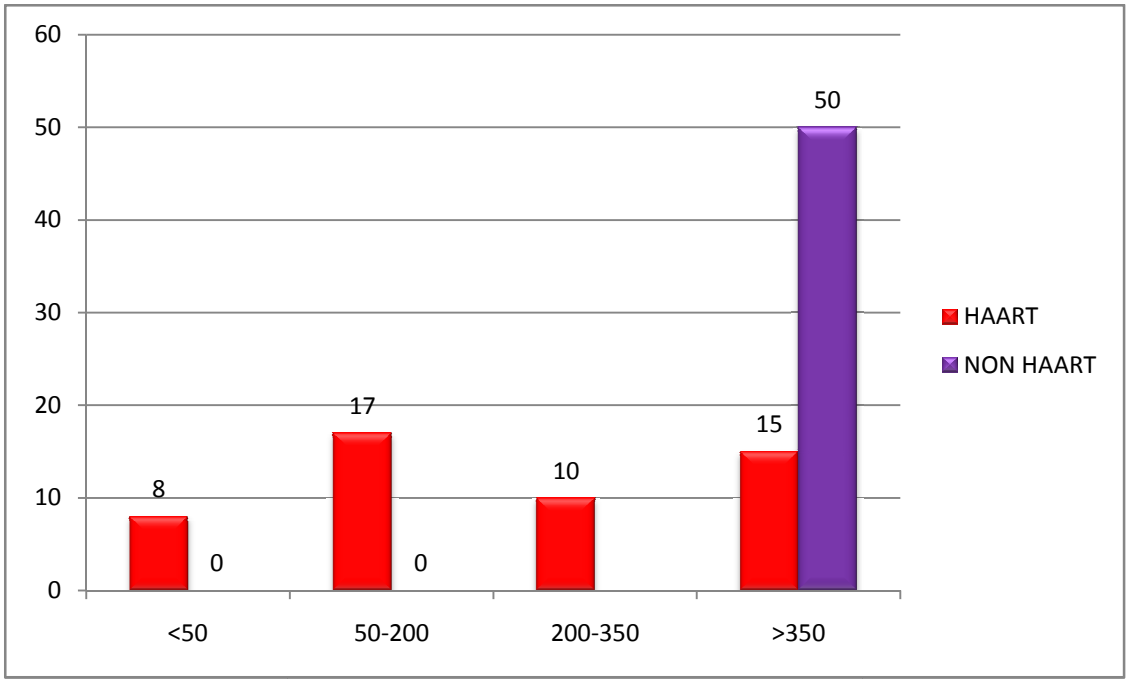


The number of alcoholics and non alcoholics in the HAART group were 8 and 42 with 16 and 84% respectively, comparatively this was 12 and 38 with 24 and 76% respectively in the non HAART group.

TABLE : 14 DISTRIBUTION OF CD 4 COUNT

CD4 COUNT	HAART	NON HAART
<50	8	0
50-200	17	0
200-350	10	0
>350	15	50

CHART : 6 DISTRIBUTION OF CD4 COUNT

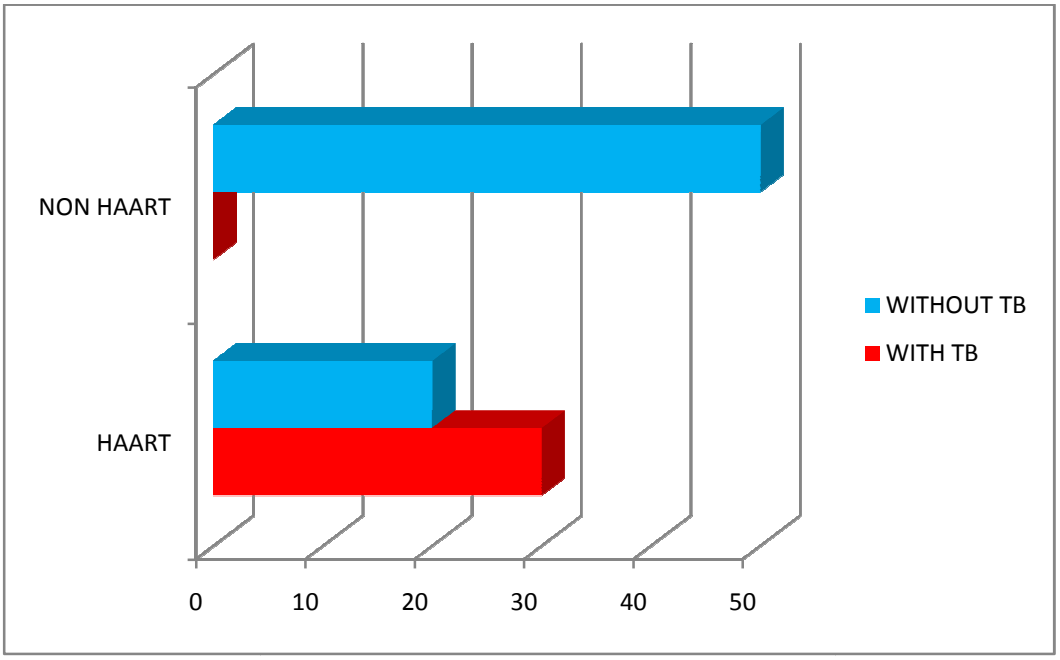


The number of patients were divided into groups in such a way that the patients in the non HAART group has a CD4 count of more than 350, whereas in the HAART group they were divided into 4 groups that is less than 50, 50 – 200, 200 – 350, more than 350.

TABLE : 15 TB AND ITS DISTRIBUTION

	HAART	NON HAART
WITH TB	30	0
WITHOUT TB	20	50

CHART : 7 PREVALENCE OF TB



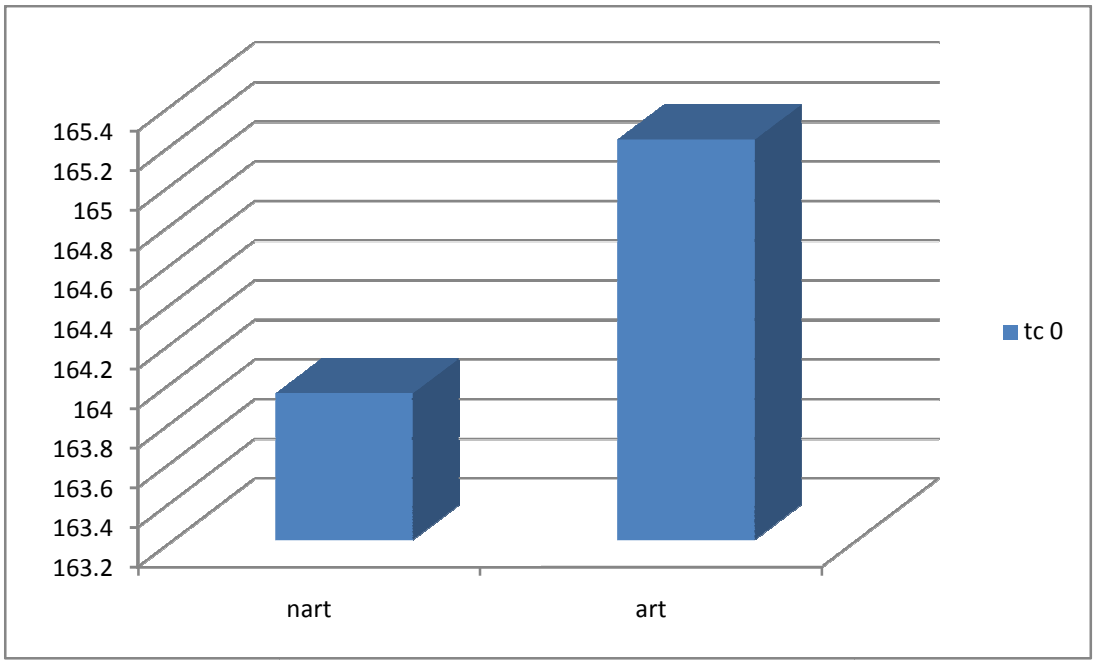
Since the prevalence of TB is very common in HIV patients it is important to describe its distribution. The patients in non HAART group has no TB, whereas the patients in HAART group infected with TB are 30 in number and the patients without TB are 20.

COMPARISON OF LIPID VALUES

TABLE: 15 TOTAL CHOLESTEROL FOR THE 0 MONTH

NON ART	163.95
ART	165.22
P VALUE	0.196

CHART: 8 TOTAL CHOLESTEROL FOR THE 0 MONTH

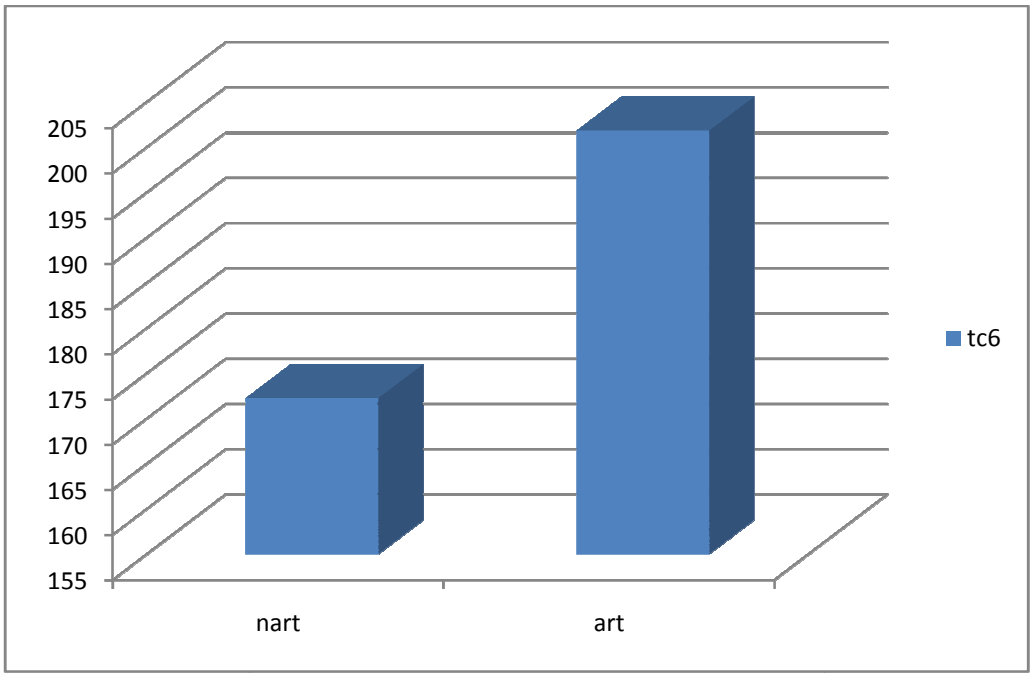


The mean value for total cholesterol for the patients on non ART and ART at the 0 month are 163.94 and 165.22, which has the p value of 0.196 which was not significant

TABLE: 16 TOTAL CHOLESTEROL FOR 6 MONTHS

NON ART	172.26
ART	201.85
P VALUE	0.000

CHART: 9 TOTAL CHOLESTEROL FOR 6 MONTHS

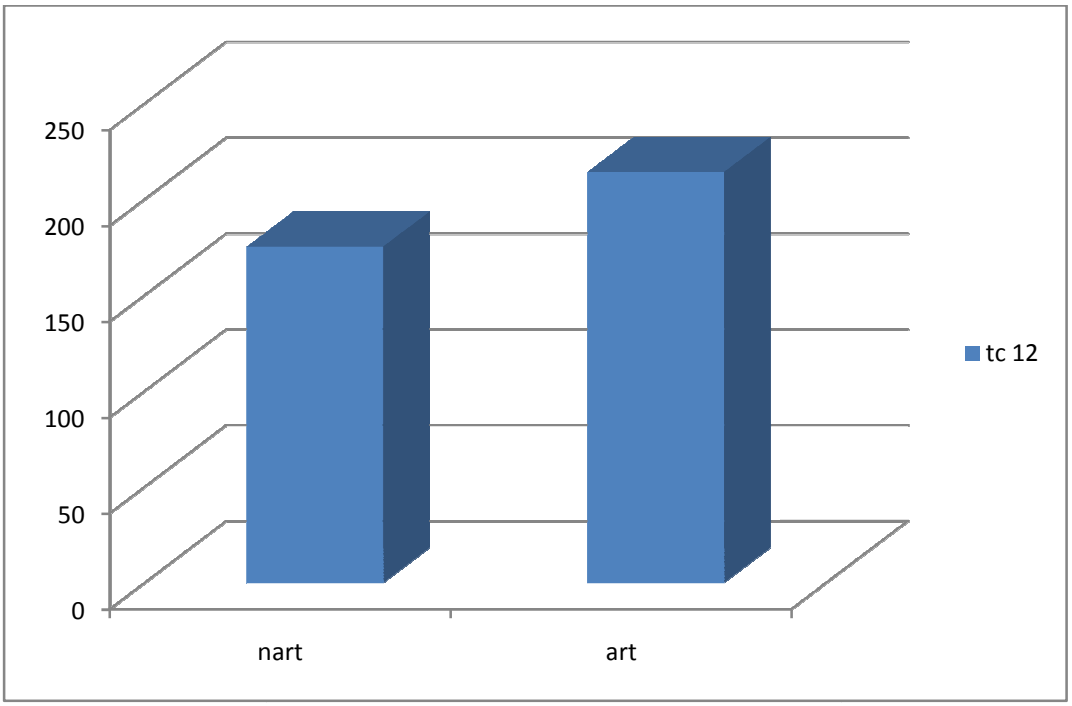


Similarly the mean value for TC at 6 months are 172.26 and 201.84 respectively which was significant with the p value of 0.000.

TABLE: 17 TOTAL CHOLESTEROL FOR 12 MONTHS

NON ART	175.25
ART	214.24
P VALUE	0.000

CHART: 10 TOTAL CHOLESTEROL FOR 12 MONTHS



The same mean at 12 months are 175.24 and 214.24 respectively with a p value significance of 0.000.

TABLE: 18 TRIGLYCERIDE FOR THE 0 MONTH

NON ART	124.79
ART	128.63
P VALUE	0.007

CHART: 11 TRIGLYCERIDE FOR THE 0 MONTH

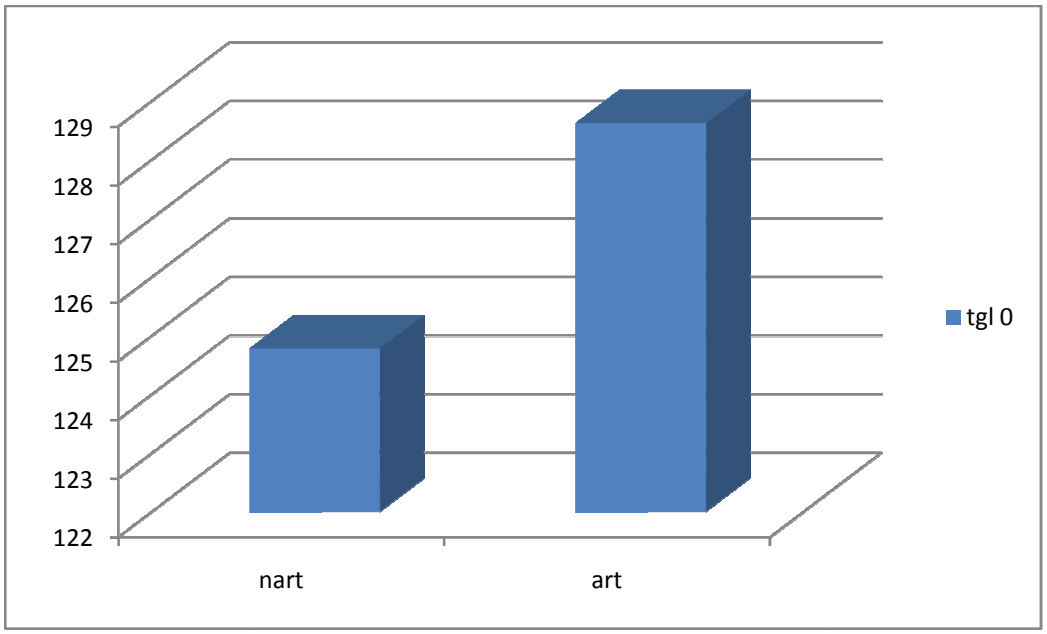


TABLE: 19 TRIGLYCERIDE FOR 6 MONTHS

NON ART	133.95
ART	152.08
P VALUE	0.000

CHART: 12 TRIGLYCERIDE FOR 6 MONTHS

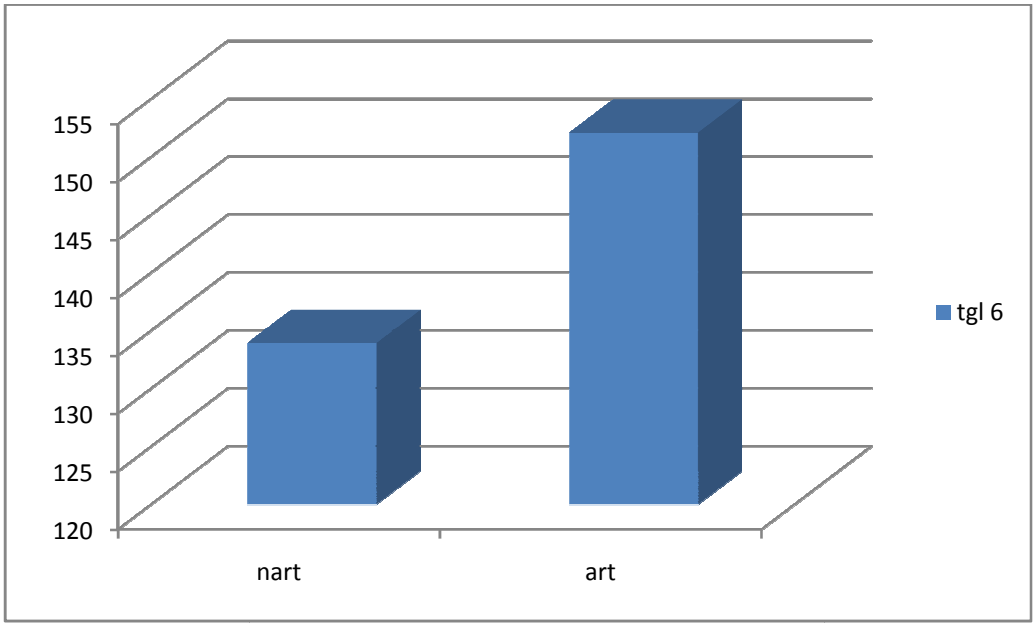
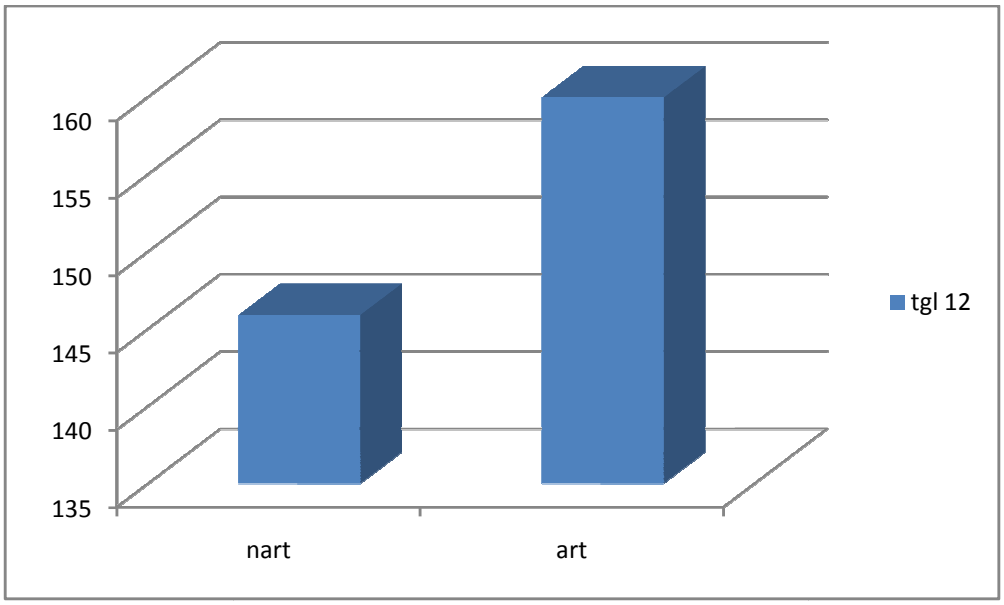


TABLE: 20 TRIGLYCERIDE FOR 12 MONTHS

NON ART	145.91
ART	159.98
P VALUE	0.000

CHART: 13 TRIGLYCERIDE FOR 12 MONTHS



Similarly the mean values for triglycerides for non ART and ART at 0 , 6, 12 months are 124.78 and 128.62, 133.94 and 152.08, 145.90 and 159.98 respectively which has a statistically significant association with p values of 0.007, 0.000, 0.000 respectively.

TABLE: 21 LDL FOR THE 0 MONTH

NON ART	98.74
ART	106.2
P VALUE	0.002

CHART : 14 LDL FOR THE 0 MONTH

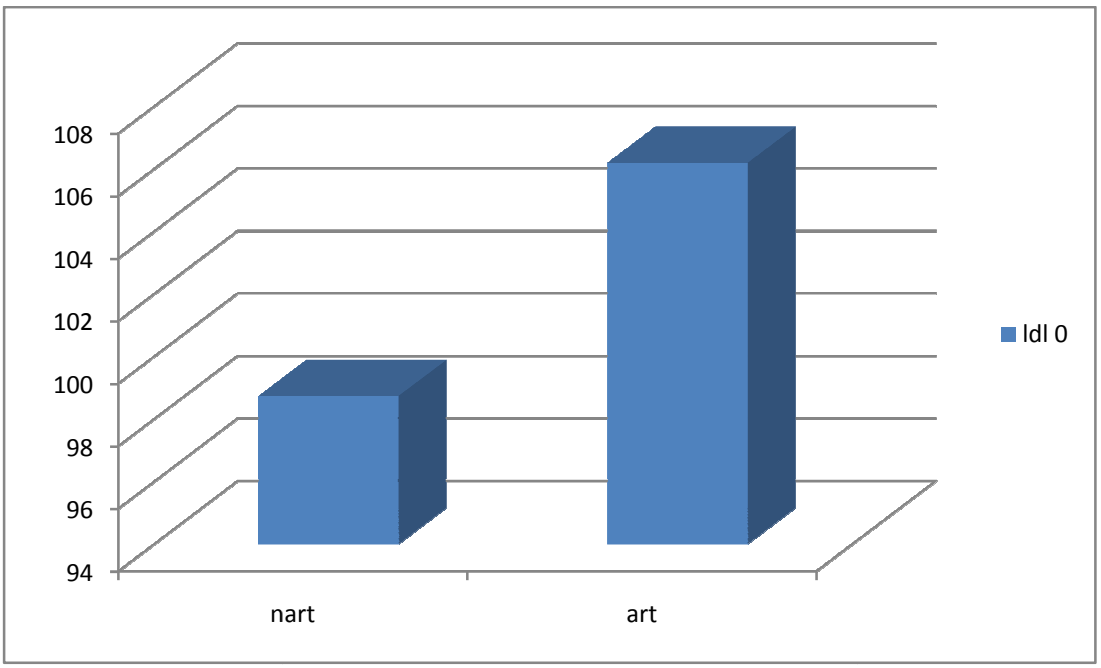


TABLE: 22 LDL FOR 6 MONTHS

NON ART	**114.48**
ART	**132.09**
P VALUE	**0.000**

CHART: 15 LDL FOR 6 MONTHS

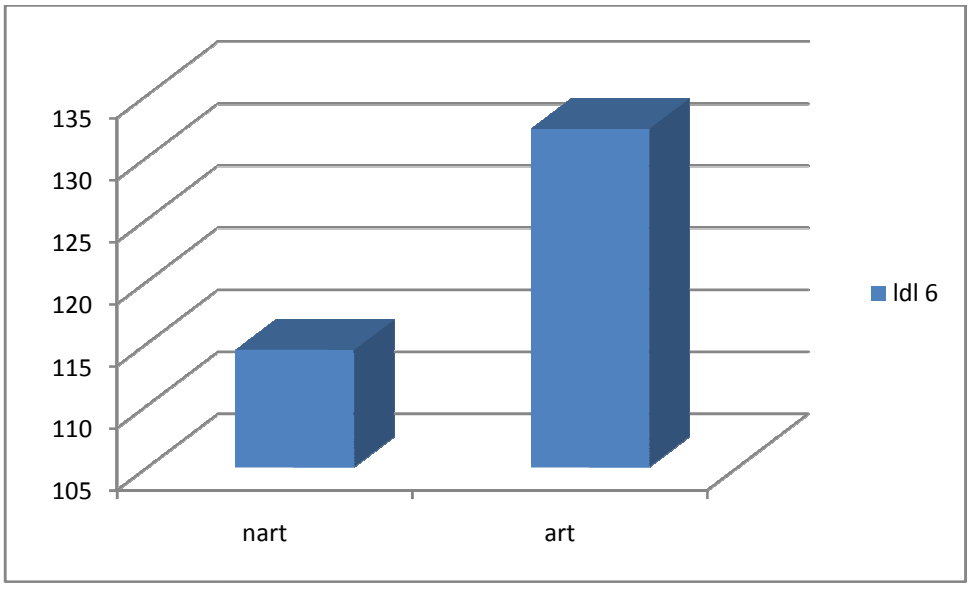
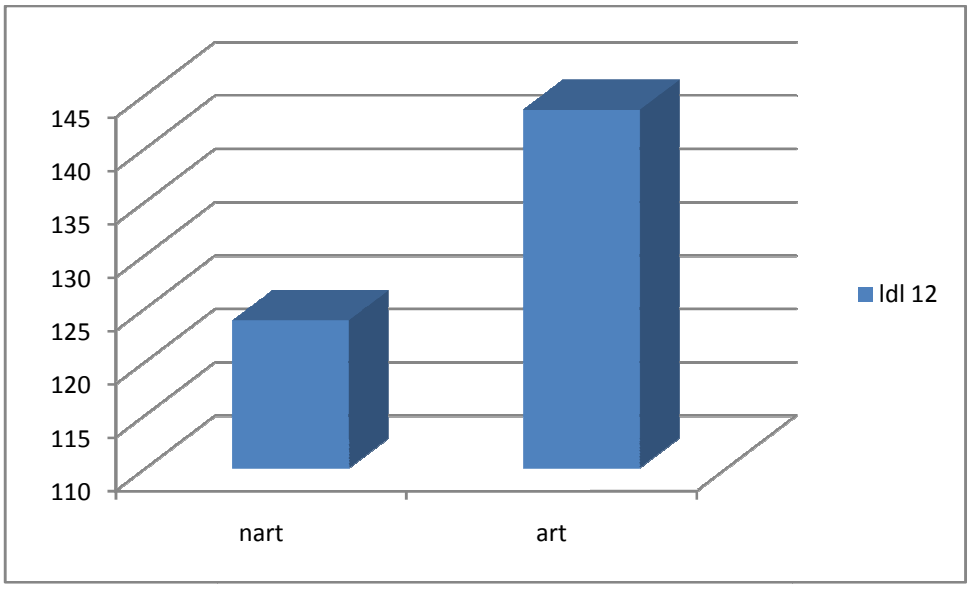


TABLE: 23 LDL FOR 12 MONTHS

NON ART	123.84
ART	143.58
P VALUE	0.000

CHART: 16 LDL FOR 12 MONTHS



The LDL cholesterol for the non ART and ART patients with the mean values at 0, 6, 12 months are 98.74 and 106.2, 114.46 and 132.26, 123.84 and 143.58 respectively, they are statistically significant with the p values with 0.002, 0.000 and 0.000.

TABLE : 24 HDL FOR THE 0 MONTH

NON ART	**43.46**
ART	**40.42**
P VALUE	**0.000**

CHART: 17 HDL FOR THE 0 MONTH

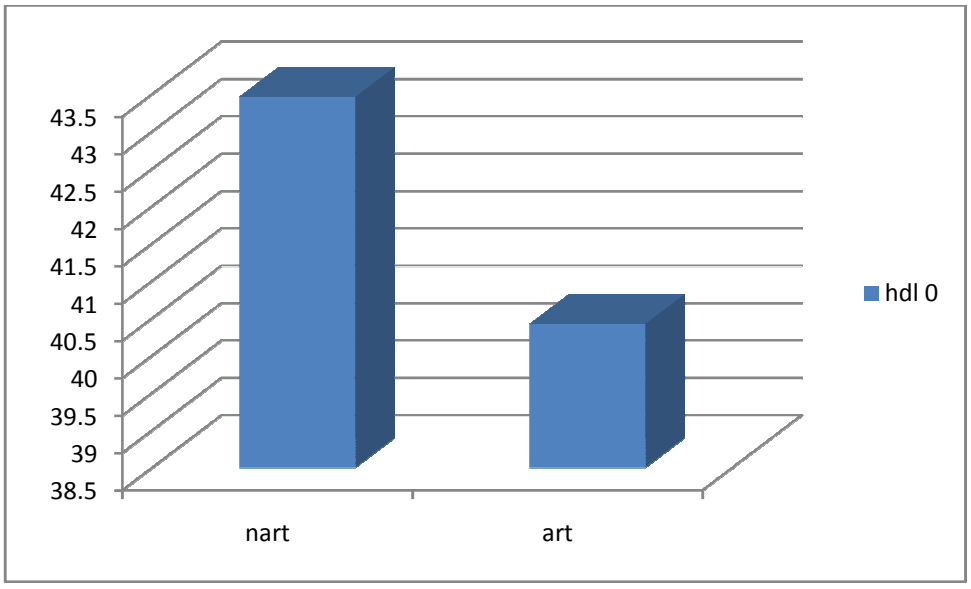


TABLE: 25 HDL FOR 6 MONTHS

NON ART	40.44
ART	38.10
P VALUE	0.000

CHART: 18 HDL FOR 6 MONTHS

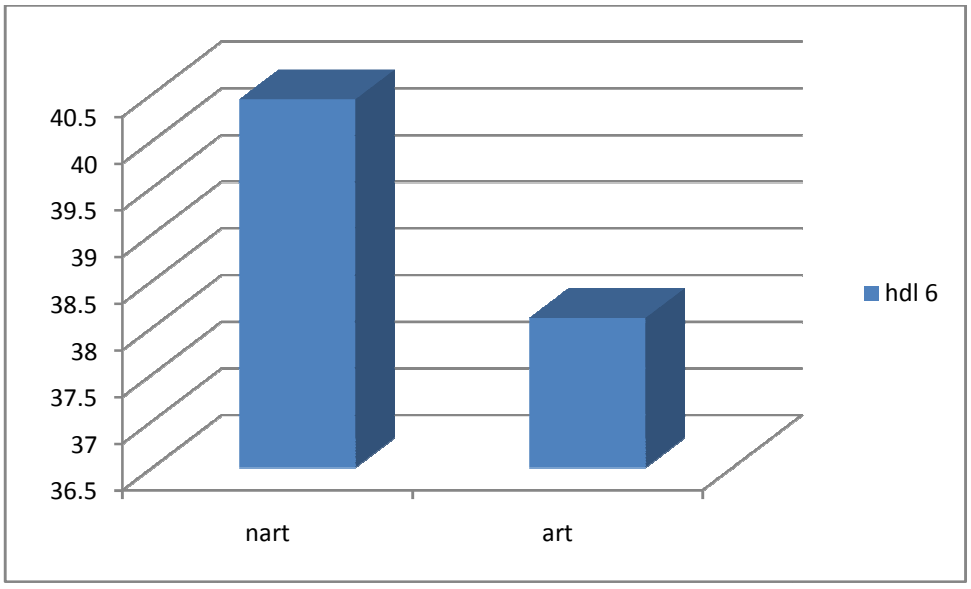
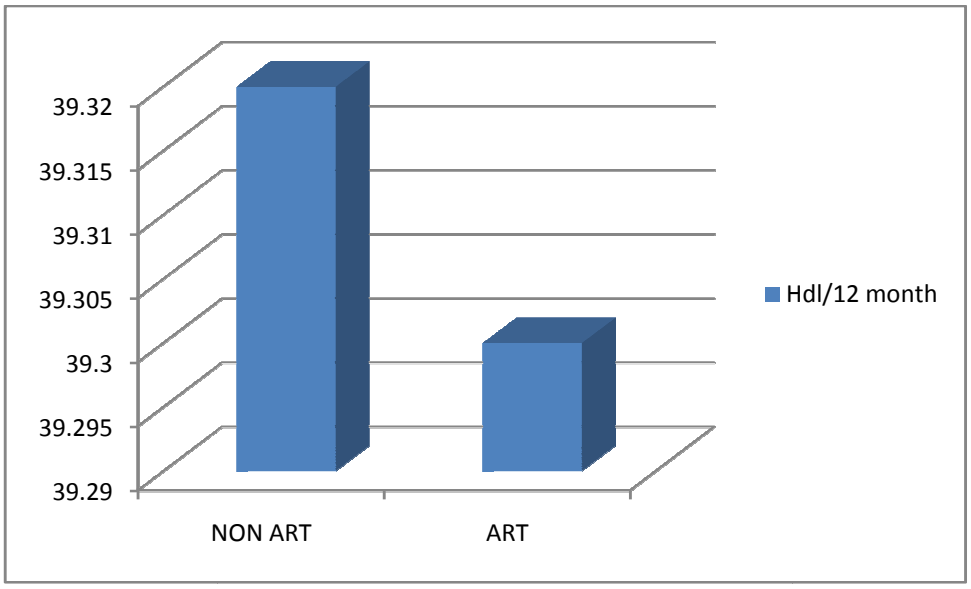


TABLE: 26 HDL FOR 12 MONTHS

NON ART	**39.32**
ART	**39.30**
P VALUE	**0.960**

CHART: 19 HDL FOR 12 MONTHS

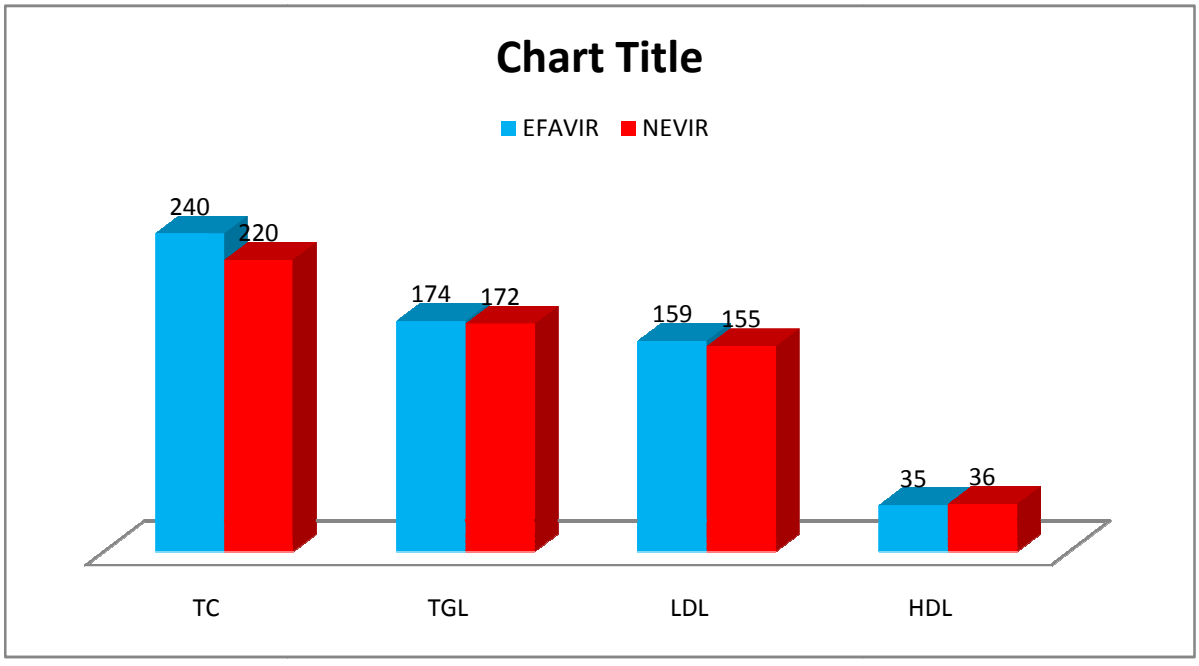


The mean values for the HDL cholesterol similarly for the non ART and ART patients for the 0, 6, and 12 months are 43.46 and 40.42, 40.44 and 38.10, 39.32 and 39.30 respectively with a p value of 0.000, 0.000 and 0.960

.TABLE: 17 COMPARISON BETWEEN EFAVIRENZ AND NEVIRAPINE

ART	EFAVIRENZ	NEVIRAPINE	P VALUE
TC	240	220	0.000
TGL	174	172	0.586
LDL	159	155	0.036
HDL	35	36	0.328

CHART: 9 COMPARISON BETWEEN EFAVIRENZ AND NEVIRAPINE



As the groups included in the ART are mainly based on Efavirenz and Nevirapine, and many studies have been dealt upon those two drugs, the comparison is done between these two groups. The mean total

cholesterol values between these two drugs are 240.43 and 220.20 which has a statistical significance p value of 0.000, the TGL mean values are 174.43 and 172.40 which was statistically insignificant with a p value of 0.586, where as the mean values of LDL between these two groups were 158.68 and 155.20 respectively which has a statistically significant p value of 0.036, finally the comparison between these two for HDL level has the mean value of 35.37 and 36.00 with a p value of 0.328 which was statistically insignificant.

DISCUSSION

DISCUSSION AND COMPARATIVE ANALYSIS

HIV as mentioned earlier is a retrovirus belonging to a subfamily of lentivirus. AIDS was first identified in united states in the year 1981. According to NACO the AIDS prevalence in India was 0.27 in the year 2013which was decreased from 0.41 in the year 2002. Since the last decade there has been a 50% decline. Also according to our NACO status India has faced a 57% reduction in annual new infections from 0.274 million in 2000 to 0.116 million in 2011. And also there is a decline in AIDS related deaths of 29% between 2007 and 2011.

First case of AIDS in India was reported in the year 1986 about 2.4 million peoples are living with this condition and about 1, 70,000 HIV/AIDS related deaths were happened.

The introduction of HAART for the sake of HIV patients had enlighten their life by the means of dramatic reduction in HIV related deaths and morbidity in each and every countries. A very strict adherence to ART will prevent the viral replication and also the effects of the disease . Because of the introduction of the HAART the quality of life of the patients was definitely improved . Even though there was a drastic change in the quality of life of the HIV patients, there occured

comorbid problems such as dyslipidemia, insulin resistance and diabetes with the long term use of HAART.

The study was conducted in Coimbatore Medical college hospital ART department for the adult patients who are at the age group of 18 to 60 years. According to this study the maximum number of patients was between 36 – 50 years. Also many other studies has showed the maximum number of patients who are affected were in these age groups. The age distribution showed a maximum prevalence in the age group of 36 to 50 years.

Coming to the sex distribution among the patients the number of male patients in the group 1 was 7 and the number of female patients was 5 with 14 and 10% respectively , with the group 2 it was 8 and 6 for males and females with 16 and 12 %. And with that of group 3 it was both 3 for males and females that constitutes about 6% each. It was 10 and 8 for the group 4 with the correspondence of 20 and 16%. Group 5 constitutes 29 males and 21 females with 58 and 42%.

In our study we have also done a marital status distribution even though it is going to be insignificant to this study, it was about 41 ART and 42 non ART are married with 82 and 84% of distribution.

Also the smoking habits were studied in the patients that the number of patients who are smokers among ART patients are 16 and to that of non ART are 21 whom are all males. According to a national survey conducted in India the percentage of smokers in India was seems to be 23% in the year 2012. Since smoking is a confounding variable the analysis was adjusted according to that.

Prevalence of alcohol in our study group are 8 persons in the HAART are alcoholics and 42 persons are non alcoholics which are 16% and 84%. In non HAART group the alcoholics are 12 in number whereas 38 are non alcoholics which are 24 and 76% respectively.

With the CD4 count all patients in the non HAART groups had the count of more than 350, the patients in the HAART group are divided into four groups, the first group which contains 8 patients has CD4 of less than 50, the second group with 17 patients has CD4 between 50-200, the third group with 10 patients has CD4 between 200-350, and the fourth group with 15 patients has CD4 count of more than 350.

Since the prevalence of TB in our country is wide spread its distribution with HIV patients are assessed. The patients with HIV had two groups with TB and the second one without TB. The first group has 30 patients and the second one has 20 patients, whereas the patients on non ART has no TB.

According to NCEP – ATP criteria the dyslipidemia is defined as TC of more than 200mg/dl, TGL of more than 150mg/dl, LDL of more than130mg/dl, HDL of less than 40mg/dl. In the present study according to the definition there should be atleast one lipid abnormality to brand as dyslipidemia.

In our study the patients in the both groups have a baseline normal lipid values, finally in the patients who are started on ART there was 26 lipid abnormalities which constitutes about 52% of the total value. Of which the Efavirenz based regimen has 16 persons with lipid abnormalities whereas the patients on Nevirapine based therapy has a lipid value abnormality of 10 persons which both constitutes 32 and 20% respectively.

According to a study conducted by Agete Tadewos et al, Zalalem Addis, Henock Ambachew and Sandip banerjee et alwhere 226 patients were involved out of which 113 were ART patients and 113 were non ART patients. In the above mentioned study 93% of the patients on HAART that is 82.3% had at least one lipid abnormality, in our study about 52% of the patients has significant lipid abnormality, in the above study conducted in Ethiopia the TC level of more than 200mg occurred in 43% of the HAART, HDL below 40 mg occurred in 44%, the low density lipoprotein elevation occurred in 34%, and the increased TGL level seen

in 55% of the patients, comparatively in our study with one year observation we have 27 patients with elevated total cholesterol level which constitutes 54%, and about 25 patients have elevated triglyceride level with 50%, whereas the LDL level was increased in 52% of the patients , finally the HDL level was decreased almost in every patients.

The mean value for the total cholesterol in the Ethiopian study group were 234.76 mgs, whereas in our study the mean value at one year was observed as 214.24mgs, following which the mean value for triglycerides in the Ethiopian group was 161.23mgs compared to a mean value of 159.98mgs in our study. When coming to the LDL level the African study has the mean value of 138mgs compared to our study which has 143.58mgs, finally to the HDL the Africans has mean value of 38.23 comparing to our study of 39.3 mgs.

In our study the association of **TC** between ART and non ART is not statistically significant at 0 month which has a p value of 0.196, whereas the association of the same at 6 and 12 months are statistically significant with a **p value of 0.000**, comparatively the **TGL** values association with ART and non ART are statistically significant with a **p value of 0.007** and a **p value of 0.000**. Also the significant association is seen with **LDL** for ART and non ART groups which has the **p value of 0.002 and 0.000.** whereas there is a statistical significant association for

HDL seen at 0 and 6 months with a **p value of 0.000**, and at one year it was 0.960 which was statistically insignificant.

As in our study where the HDL values are statistically insignificant with a p value of >0.05 at the end of one year, another study conducted at Nigeria by Francis M.Awah et al and Onyine Agughasi et al with 50 patients that 25 on ART and 25 not on ART also has the same outcome in which there was statitically significant p value association seen with that of TC, TGL, LDL but not with that of HDL where there was a statistical insignificance with a p value of >0.05.

Since we are discussing about many studies conducted in various countries it is also very important to know about the studies done in india. A study was conducted by RAB Carey, P Rupali, OC Abraham, D Kattula at Christian medical College, Vellore regarding the prevalence of cardiovascular risk factors in Indian patients using first line ART, it showed

	HIV pts on ART	**HIV pts not on ART**
TC	**195.60**	**151.47**
TGL	**268.34**	**121.57**
HDL	**42.38**	**32.55**
LDL	**106.36**	**93.24**

It was discussed from this study that there are limited data from the developing countries like India where most of the patients was on first line ART, from this study it was found that there was an increased prevalence of dyslipidemia in the patients who are in first line antiretroviral therapy.

Since many studies that was conducted in developed countries are mainly with that of protease inhibitors, the above mentioned study was dealt with first line ART that too with NRIs and NNRIs.

In this study there was high prevalence of hypercholesterolemia and hypertriglyceredemia and there was a low prevalence for low HDL, comparatively in our study also there was high prevalence of hypercholesterolemia and hypertriglyceredemia and also in addition there was high prevalence of low HDL.

By these data it is clear that due to prevalence of dyslipidemia there will be a definite increase risk in cardio and cerebrovascular complications among our Indian population.

In comparison for the Efavirenz and Nevirapine the lipid profile derangements were extensively studied. In the studies conducted by Frank van leth et al, Prahpanphanuphak et al the lipid derangements with that of efavirenz was very much increased compared to nevirapine. The

total cholesterol and triglycerides were increased by efavirenz whereas HDL was increased by nevirapine . In our study there was a statistically significant difference in total cholesterol values at one year with **a p** value of **0.000** even though both the drugs increased the total cholesterol value, regarding the LDL value also there occurs a significant association with the **p value of <0.05** even though both the drugs had increased the LDL values, but in comparison of HDL value to that of the study our study tend to decrease the HDL values with the usage of these two drugs.

Another study done by Jane A o Halloran et al, Claudette S Satchell and Patrick mallon et al found that there is significant rise in TC and TGL values when the patients are started with efavirenz when compared to nevirapine.

Coming to the zidovudine and tenofovir we have not compared the actual lipid derangements between these two groups, but there were studies showing that tenofovir tends to increase a little bit rise in total cholesterol and low density lipoprotein in comparison with that of zidovudine. This was studied by Gallant JE, Dejesus E and Arribas JR et al, but in contrast to this study many studies founded that tenofovir has a favourable lipidprofile compared to that of zidovudine. In the study done in Hawassa , southern Ethiopia the lipid profile derangements between these two drugs were as follows

LIPID PROFILE	ZDV BASED n = 58 (%)	TEN BASED n = 55 (%)	P value
TC> 200 mg	25 (43.1)	24 (43.6)	0.95
HDL< 40 mg	24 (41.4)	25 (45.4)	0.66
LDL> 130 mg	20 (34.5)	18 (32.7)	0.84
TGL > 150 mg	32 (55.2)	31 (56.4)	0.41

So in this study when compared to previous study the lipid abnormalities are almost equal with a slight upper hand with that of zidovudine , but however there is no significant difference in lipid abnormalities between these two.

The same study groups at Hawassa, Southern Ethiopia was compared for nevirapine and efavirenz which the results came as follows

LIPID PROFILE	EFV BASED n = 46 (%)	NVP BASED n = 67 (%)
TC> 200 mg	18 (39.1)	31 (46.3)
HDL< 40 mg	22 (47.8)	27 (40.3)
LDL> 130 mg	14 (30.4)	24 (35.8)
TGL > 150 mg	25 (54.3)	38 (56.7)

In the above study even though the study group of the nevirapine group was one third more than that of efavirenz there is no significant difference in abnormality in lipid parameters in between these groups. In the study done in our hospital, the comparison between efavirenz and nevirapine is as follows, the TC for efavirenz at 1 year study has a mean value of 240.4 and 220.2 for nevirapine with a statistical significant association of **0.000**, similarly the mean value for TGL for both of these drugs are 174.43 and 172.40 which has no association with a p value of 0.586, the same mean for LDL at the 1 year has the mean value of 158.68 and 155.20 with a significant p value of **0.036**, finally the mean value of HDL between these two drugs was of 35.37 and 36.00 with no significant association with a p value of 0.328 .

	EFV	**NVP**	**p value**
TC	**240.43**	**220.20**	**0.000**
TGL	**174.43**	**172.4**	**0.586**
LDL	**155.20**	**155.2**	**0.036**
HDL	**35.37**	**36.00**	**0.328**

CONCLUSION

1. As observed by the study there are significant lipid abnormalities in patients on HAART.
2. There is a statistically significant increase in total cholesterol, triglycerides, low density lipoproteins among the HAART patients at the end of one year.
3. However there is statistically insignificant decrease in high density lipoproteins in HIV infected patients on HAART.
4. In comparison with efavirenz and nevirapine there is a statistical significant difference between these two with a increased incidence of dyslipidemia in efavirenz based regimen.
5. Protease inhibitors which causes more lipid abnormalities than NRTIs and NNRTIs was not included, because it comes under second line regimen which is not used in our institution.

SUMMARY

The main aim of this study is to determine the prevalence of dyslipidemia among the HIV patients using first line HAART. Since many studies has found that the incidence and prevalence of dyslipidemia among HAART users are increasing it is very important to find our patients living in and around our city living with dyslipidemia. By finding the lipid abnormalities we can try to decrease the incidence of cardiovascular and cerebrevascular complications.

Out of 100 patients included in our study , we compared 50 patients were already on HAART and 50 patients not yet started on HAAR. The ART regimen was initiated according to the WHO guidelines. The patients who were exposed to HAART for a minimum of 2 years were selected in our treatment group. They were distributed according to their age, sex, marital status, CD4 count , smoking and alcohol habits and prevalence of TB.

From the results obtained in our study it is clear that the prevalence of dyslipidemia(elevated TC, TGL and LDL) was higher in patients on ART when compared to patients not on ART (p value < 0.001). There was no difference in the prevalence of HDL. Even though both efavirenz and nevirapine had an impact over lipid profile, the prevalence of dyslipidemia was more with efavirenz.

In conclusion by monitoring the lipid parameters in HIV patients to be started on HAART, we can start them with lipid friendly drugs if there is associated dyslipidemia, on the other hand the patients with dyslipidemia who was already on HAART can be switched over to lipid friendly regimens or we can add lipid lowering drugs . So by doing this we can at least prevent or reduce cardio and cerebrovascular complications and thereby we can improve the quality of life in patients who are already immunocompromised.

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INFORMED CONSENT

DEPARTMENT OF GENERAL MEDICINE

Coimbatore Medical College, Coimbatore

Principal investigator : Dr. Karthikeyan .N

Research guide : Dr. M.Raveendran M.D.

Organization : Department of General Medicine

Informed consent : I have been invited to participate in research Project titled **'PREVALENCE OF DYSLIPIDEMIA AMONG HIV INFECTED PATIENTS USING FIRST LINE HAART IN COIMBATORE MEDICAL COLLEGE HOSPITAL'**

I understand, it will be answering a set of questionnaire, undergo physical examination, investigations and appropriate treatment.

I also give consent to utilize my personal details for study purpose and can be contacted if necessary.

I am aware that I have the right to withdraw at any time which will not affect my medical care.

Name of the participant:

Signature:

Date

ஒப்புதல் படிவம்

பெயர் :

பாலினம் :

முகவரி : வயது :

அரசு கோவை மருத்துவக் கல்லூரியில் பொது மருத்துவ துறையில் பட்ட மேற்படிப்பு பயிலும் மாணவர் **மரு.நா. கார்த்திகேயன்** அவர்கள் மேற்கொள்ளும் "**கோயமுத்தூர் மருத்துவ கல்லூரி மருத்துவமனையில் எச் ஐ வி நோயினால் பாதிக்கப்பட்ட நோயாளிகளுக்கு முதல் நிலை ART மருந்து கொடுப்பதினால் இரத்தத்தில் உள்ள கொழுப்பின் அளவில் ஏற்படும் மாறுதல் பற்றிய** " ஆய்வில் செய்முறை மற்றும் அனைத்து விவரங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுபடுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடன், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னுடைய அனைத்து விபரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக்கொள்கிறேன். எந்த நேரத்தில் அந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் : கையொப்பம் / ரேகை

நாள் :

PROFORMA

Name :CD4 count :

Age :

Sex :

IP NO :

BMI :

Marital status :

Smoking habits :

History of Diabetes :

Hypertension :

CAD :

CRF :

Dyslipidemia :

Tuberculosis :

Alcoholism :

Treatment groups :

Group I -

Group II -

Group III -

Group IV -

Group V -

LIPID PROFILE :

	HAART GROUP			NON-HAART GROUP		
	O M	6 M	12 M	O M	6 M	12 M
TC						
TGL						
LDL						
HDL						

KEY TO MASTER CHART

1. 1 - Z L N

2. 2 - Z L E

3. 3 - T L N

4. 4 - T L E

5. 5 - NON – A R T

6. UM - Unmarried

7. M - Married

8. S - Smoker

9. NS - Non Smoker

10. A - Alcoholic

11. B - Non Alcoholic

12. C - CD 4 more than 350

13. Y - Yes

14. N - No

S.No	AGE	SEX	GRP	MARR	SMOKE	ALCOH	CD4	TB	TC			TGL			LDL			HDL		
									0 MO	6 MO	12 MO	0 MO	6 MO	12 MO	0 MO	6 MO	12 MO	0 MO	6 MO	12 MO
1	20	M	5	UM	NS	B	C	N	161	170	174	125	132	155	100	110	125	44	41	37
2	23	M	5	UM	S	A	C	N	164	165	172	123	135	136	110	112	124	43	40	38
3	33	F	5	M	NS	B	C	N	168	168	175	134	136	149	102	114	122	45	41	39
4	34	F	5	M	NS	B	C	N	160	171	189	114	138	145	102	117	128	46	40	41
5	45	M	5	M	S	B	C	N	163	169	165	135	146	156	107	118	127	41	40	38
6	31	M	5	M	NS	A	C	N	165	170	178	116	126	170	106	131	126	47	40	42
7	30	M	5	UM	S	B	C	N	168	198	172	117	156	143	104	101	124	40	42	39
8	26	F	5	M	NS	B	C	N	166	165	186	134	116	141	102	128	121	42	41	38
9	23	F	5	UM	NS	B	C	N	165	170	175	125	131	142	100	99	122	43	40	41
10	28	F	5	UM	NS	B	C	N	169	171	179	126	137	143	92	110	125	44	42	42
11	35	M	5	M	S	A	C	N	160	174	165	128	130	159	112	114	122	46	40	39
12	35	M	5	M	NS	B	C	N	162	175	185	130	131	141	101	118	124	44	41	44
13	31	F	5	M	NS	B	C	N	163	187	176	123	132	134	89	117	124	41	40	36
14	44	M	5	M	S	A	C	N	166	170	186	123	131	168	101	114	124	42	40	35
15	30	M	5	M	NS	B	C	N	166	173	166	126	139	132	101	110	136	43	40	45
16	22	M	5	UM	S	B	C	N	167	174	190	140	131	155	96	113	128	46	40	38

17	27	M	5	UM	S	A	C	N	161	170	156	112	132	143	101	112	127	47	42	37
18	39	F	5	M	NS	B	C	N	164	168	176	126	134	146	96	116	122	48	45	39
19	44	F	5	M	NS	B	C	N	163	181	165	127	131	147	15	117	127	43	44	39
20	42	M	5	M	S	B	C	N	164	188	185	128	131	148	98	113	123	42	39	39
21	38	M	5	M	NS	B	C	N	166	171	190	130	130	146	104	110	120	40	40	39
22	21	M	5	UM	S	A	C	N	164	176	160	129	131	146	87	130	121	43	40	41
23	43	F	5	M	NS	B	C	N	167	178	171	122	140	144	119	102	121	44	44	42
24	47	M	5	M	S	B	C	N	161	171	175	122	121	143	102	87	127	46	36	38
25	48	F	5	M	NS	B	C	N	160	173	177	124	140	146	101	119	112	42	44	38
26	50	M	5	M	NS	A	C	N	164	172	174	121	121	170	104	115	125	44	41	39
27	38	M	5	M	S	B	C	N	163	190	178	118	150	124	87	114	124	46	39	41
28	39	M	5	M	NS	B	C	N	162	181	179	140	118	130	91	117	126	41	38	41
29	39	M	5	M	S	B	C	N	169	162	176	136	131	151	114	112	121	40	39	42
30	42	M	5	M	NS	A	C	N	170	167	174	112	134	138	98	113	122	44	41	38
31	41	F	5	M	NS	B	C	N	165	162	176	110	130	165	118	116	122	43	41	39
32	40	F	5	M	NS	B	C	N	178	168	179	127	135	141	78	114	126	43	42	37
33	39	F	5	M	NS	B	C	N	145	170	180	128	131	140	91	117	123	44	38	43
34	23	M	5	UM	S	B	C	N	160	170	160	112	130	141	99	118	110	42	42	39
35	47	M	5	M	S	A	C	N	171	145	176	122	137	147	107	113	140	46	38	39

36	39	F	5	M	NS	B	C	N	134	186	177	123	137	145	104	115	123	44	40	41
37	45	M	5	M	S	B	C	N	181	156	177	124	138	146	101	114	138	43	40	39
38	47	M	5	M	S	A	C	N	162	189	176	127	140	142	100	118	112	43	42	41
39	49	F	5	M	NS	B	C	N	165	171	178	125	121	144	91	120	1227	41	38	39
40	56	F	5	M	NS	B	C	N	164	172	179	128	159	141	92	121	126	42	40	38
41	54	M	5	M	S	B	C	N	161	175	176	124	118	140	94	117	122	43	42	39
42	57	M	5	M	S	B	C	N	160	171	180	127	137	165	107	112	128	44	41	37
43	58	M	5	M	S	A	C	N	162	173	160	130	134	134	101	114	123	46	39	41
44	60	F	5	M	NS	B	C	N	163	172	181	118	130	146	100	116	127	41	40	39
45	51	M	5	M	S	A	C	N	167	181	164	122	132	144	81	117	124	43	41	39
46	54	M	5	M	S	B	C	N	168	151	177	126	130	148	121	118	124	45	38	38
47	57	F	5	M	NS	B	C	N	165	170	179	124	160	149	91	120	110	42	42	37
48	59	F	5	M	NS	B	C	N	164	172	174	127	138	141	118	112	122	45	41	39
49	53	F	5	M	NS	B	C	N	166	180	170	123	134	147	101	110	124	44	39	38
50	55	F	5	M	NS	B	C	N	165	161	174	126	135	138	100	118	126	42	38	39
51	23	F	3	UM	NS	B	260	N	167	202	198	127	158	178	118	137	151	43	38	38
52	41	M	4	M	S	B	45	N	168	204	235	134	138	144	108	129	156	42	43	37
53	33	F	1	M	NS	B	90	Y	169	198	223	124	175	176	114	136	129	40	37	41
54	22	M	2	UM	NS	B	300	N	170	211	235	127	134	148	108	127	159	41	42	39

55	24	F	1	UM	NS	B	154	Y	164	205	224	127	154	149	107	140	156	41	37	42
56	26	M	3	M	NS	B	348	Y	163	192	200	126	158	140	114	128	128	42	37	38
57	31	F	1	M	NS	B	111	N	167	207	231	123	156	165	108	128	149	41	40	39
58	26	F	4	UM	NS	B	85	Y	165	208	265	124	141	186	100	130	161	40	41	38
59	29	F	2	M	NS	B	167	Y	167	212	256	128	162	178	102	140	128	42	43	41
60	24	M	1	UM	NS	B	90	N	164	210	212	126	158	149	111	139	154	41	37	42
61	36	M	3	M	S	B	48	Y	167	201	231	122	155	148	105	140	153	41	42	44
62	27	M	2	UM	S	B	250	Y	165	196	238	127	170	175	108	129	158	40	37	39
63	34	F	1	M	NS	B	49	Y	169	278	197	126	156	144	118	141	129	41	36	36
64	31	F	1	UM	NS	B	145	N	166	189	210	127	145	140	103	127	152	41	37	35
65	48	M	4	M	S	B	275	Y	162	207	234	123	170	180	98	128	129	36	35	38
66	43	M	3	M	S	B	35	Y	161	203	220	128	139	144	99	133	129	40	41	45
67	36	F	4	M	NS	B	156	Y	165	198	236	118	160	165	106	141	127	40	37	39
68	41	F	1	M	NS	B	240	Y	167	206	213	121	147	175	108	136	162	38	38	37
69	45	F	2	M	NS	B	195	N	165	208	238	120	148	149	98	145	158	41	36	39
70	50	M	1	M	S	B	90	Y	167	198	196	129	161	149	114	127	129	40	37	39
71	49	F	4	M	NS	B	48	Y	164	208	238	131	164	148	106	130	130	36	37	39
72	37	M	1	M	S	B	104	N	164	197	228	129	142	170	110	136	155	42	42	42
73	39	F	4	M	NS	B	248	N	165	193	197	126	149	148	108	132	126	40	36	41

74	24	M	1	UM	S	A	90	Y	167	201	187	128	138	168	107	121	165	40	41	39
75	40	F	2	M	NS	B	40	Y	161	187	190	124	148	148	110	131	127	41	37	38
76	43	F	3	M	NS	B	89	N	165	201	210	126	141	178	103	128	130	40	36	38
77	50	F	4	M	NS	B	275	Y	164	209	265	132	175	168	104	137	129	41	37	41
78	38	M	1	M	S	A	78	N	169	199	195	134	135	167	107	129	155	42	34	42
79	37	F	2	M	NS	B	296	Y	164	198	190	132	149	187	106	127	156	36	42	38
80	33	F	1	M	NS	B	42	N	164	195	186	132	149	148	101	137	129	40	41	41
81	48	M	2	M	NS	A	95	Y	163	208	198	128	164	181	100	135	129	41	33	37
82	45	F	2	M	S	B	80	Y	164	198	189	127	133	178	109	137	165	42	35	43
83	48	F	3	M	NS	B	325	Y	165	208	196	128	144	171	102	129	128	41	42	39
84	49	F	2	M	NS	B	175	Y	168	195	199	127	148	149	110	128	130	40	40	41
85	36	M	4	M	S	B	134	Y	164	203	195	127	162	170	104	135	161	40	34	39
86	39	M	2	M	NS	A	143	Y	165	198	200	127	149	150	107	129	127	41	41	41
87	50	M	4	M	S	B	40	N	166	209	198	124	164	166	103	129	130	41	37	39
88	44	M	2	M	S	B	97	Y	164	207	198	127	149	170	104	128	156	40	34	39
89	41	M	4	M	NS	A	198	N	164	207	256	126	162	175	107	136	129	41	42	38
90	44	M	4	M	NS	B	173	Y	165	198	190	128	158	180	110	128	156	42	43	39
91	48	M	4	M	S	B	102	Y	167	198	236	125	144	156	107	129	156	41	33	37
92	59	M	2	M	NS	A	87	Y	169	198	232	137	160	148	103	124	156	40	34	41

93	51	M	4	M	S	B	134	Y	167	186	210	154	161	148	104	130	130	41	35	39
94	60	M	4	M	NS	B	145	Y	166	175	198	141	141	149	107	133	161	40	36	38
95	58	M	2	M	S	A	75	N	164	198	175	131	148	149	110	128	128	41	39	39
96	53	M	2	M	NS	B	187	N	165	199	240	132	163	140	104	138	161	38	37	37
97	55	M	4	M	NS	A	156	N	161	200	234	130	144	142	109	129	129	40	39	38
98	58	M	4	M	NS	B	145	N	166	187	198	156	147	149	91	138	164	40	38	39
99	59	M	4	M	NS	B	75	N	163	193	196	114	143	144	100	128	129	41	40	39
100	60	F	4	M	NS	B	100	N	160	206	196	141	145	172	101	133	155	41	39	38